

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
25 October 2001 (25.10.2001)

PCT

(10) International Publication Number
WO 01/79167 A2

(51) International Patent Classification⁷: C07D 207/00

(21) International Application Number: PCT/US01/12333

(22) International Filing Date: 12 April 2001 (12.04.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/197,796	14 April 2000 (14.04.2000)	US
60/198,497	18 April 2000 (18.04.2000)	US

(71) Applicant: AGOURON PHARMACEUTICALS, INC.
[US/US]; 10350 North Torrey Pines Road, La Jolla, CA
92037 (US).

(72) Inventors: JOHNSON, Theodore, O., Jr.; 3612 Torrey
View Court, San Diego, CA 92130 (US). HUA, Ye; 8671
Via Mallorca, Apt. #46, La Jolla, CA 92037 (US). LUU,
Hiep, T.; 10330 Penrod Lane, San Diego, CA 92126
(US). DRAGOVICH, Peter, S.; 1372 Blue Heron Avenue,
Encinitas, CA 92024 (US).

(74) Agents: SIEBURTH, Kathryn, L. et al.; Fitzpatrick,
Cella, Harper & Scinto, 30 Rockefeller Plaza, New York,
NY 10112-3801 (US).

(81) Designated States (*national*): AF, AG, AI, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GI, GM,
HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK,
LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX,
MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL,
TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

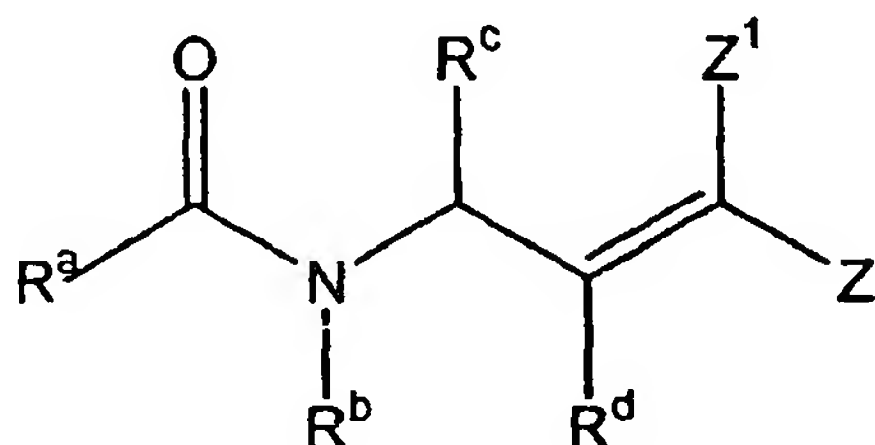
(84) Designated States (*regional*): ARIPO patent (GI, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished
upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: ANTIPICORNAVIRAL COMPOUNDS AND COMPOSITIONS, THEIR PHARMACEUTICAL USES, AND MATE-
RIALS FOR THEIR SYNTHESIS



(I)

(57) Abstract: Compounds of the formula (I) where the formula variables are as defined in the disclosure, advantageously inhibit or block the biological activity of the picornaviral 3C protease. These compounds, as well as pharmaceutical compositions containing these compounds, are useful for treating patients or hosts infected with one or more picornaviruses, such as RVP. Intermediates and synthetic methods for preparing such compounds are also

described.

- 1 -

TITLE

ANTIPICORNAVIRAL COMPOUNDS AND COMPOSITIONS,
THEIR PHARMACEUTICAL USES, AND
5 MATERIALS FOR THEIR SYNTHESIS

BACKGROUND OF THE INVENTION

Field of the Invention

10 The invention relates to pyrrole-containing peptidomimetic compounds that inhibit the enzymatic activity of picornaviral 3C proteases, especially rhinovirus 3C proteases (RVPs), and that retard viral growth in cell culture. The invention also relates to the use of these compounds in pharmaceutical compositions, methods of treatment of rhinoviral infections using these compounds and compositions, and
15 processes for the synthesis of these compounds and compounds useful in the syntheses thereof.

Related Background Art

20 The picornaviruses are a family of tiny non-enveloped positive-stranded RNA-containing viruses that infect humans and other animals. These viruses include the human rhinoviruses, human polioviruses, human coxsackieviruses, human echoviruses, human and bovine enteroviruses, encephalomyocarditis viruses,

- 2 -

meningitis virus, foot and mouth viruses, hepatitis A virus, and others. The human rhinoviruses are a major cause of the common cold. To date, there are no effective therapies on the market that cure the common cold, only treatments that relieve the symptoms.

5 Picornaviral infections may be treated by inhibiting the proteolytic picornaviral 3C enzymes. These enzymes are required for the natural maturation of the picornaviruses. They are responsible for the autocatalytic cleavage of the genomic, large polyprotein into the essential viral proteins. Members of the 3C protease family are cysteine proteases, where the sulfhydryl group most often cleaves the
10 glutamine-glycine amide bond. Inhibition of 3C proteases is believed to block proteolytic cleavage of the viral polyprotein, which in turn can retard the maturation and replication of the viruses by interfering with viral particle production. Therefore, inhibiting the processing of this cysteine protease with selective small molecules that are specifically recognized should represent an important and useful approach to treat
15 and cure viral infections of this nature and, in particular, the common cold.

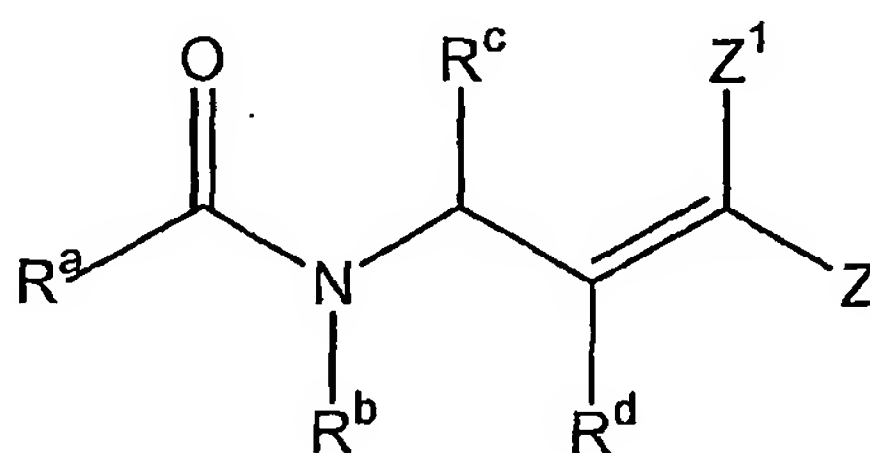
 Some small-molecule inhibitors of the enzymatic activity of picornaviral 3C proteases (i.e., antipicornaviral compounds) have been recently discovered. See, for example: U.S. Patent No. 5,856,530; U.S. Patent No. 5,962,487; U.S. Patent No. 6,020,371; and U.S. Patent Application No. 09/301,977, filed April 29, 1999, by
20 Dragovich et al. See also: Dragovich et al., "Structure-Based Design, Synthesis, and Biological Evaluation of Irreversible Human Rhinovirus 3C Protease Inhibitors . . . ,"
J. Med. Chem. (1999), Vol. 42, No. 7, 1203-1212, 1213-1224; and Dragovich et al., "Solid-phase Synthesis of Irreversible Human Rhinovirus 3C Protease Inhibitors . . . ,"
Bioorg. & Med. Chem. (1999), Vol. 7, 589-598. There remains a desire, to discover
25 small-molecule compounds that are especially potent antipicornaviral agents.

 Inhibitors of other related cysteine proteases such as cathepsins have been described in, e.g., U.S. Patent No. 5,374,623; U.S. Patent No. 5,498,616; and WIPO International Publication Nos. WO 94/04172, WO 95/15749, WO 97/19231, and WO 97/49668. There yet remains a need for inhibitors targeting the picornaviral 3C
30 cysteine protease with desirable pharmaceutical properties, such as high specificity, good therapeutic index or low toxicity.

- 3 -

SUMMARY OF THE INVENTION

This invention relates to compounds useful for inhibiting the activity of picornaviral 3C proteases having the general Formula I:



I

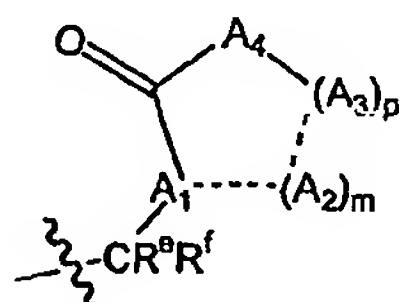
wherein:

10 R^a is an alkylcarbonylalkyl, cycloalkylcarbonylalkyl, arylcarbonylalkyl, heteroarylcarbonylalkyl, alkylcarbonylaminoalkyl, cycloalkylcarbonylaminoalkyl, heterocycloalkylcarbonylaminoalkyl, arylcarbonylaminoalkyl, heteroarylcarbonylaminoalkyl, alkylaminocarbonylalkyl, cycloalkylaminocarbonylalkyl, heterocycloalkylaminocarbonylalkyl, arylaminocarbonylalkyl, heteroarylaminocarbonylalkyl group, where each alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl moiety thereof is unsubstituted or substituted with one or more suitable substituents;

R^b is H or an alkyl group, unsubstituted or substituted with one or more suitable substituents;

20 R^d is H, halo, hydroxyl, or an alkyl, alkoxy or alkylthio group, where the alkyl, alkoxy or alkylthio group is unsubstituted or substituted with one or more suitable substituents;

R^c is a moiety having the formula:



25 R^e and R^f are each independently H or a lower alkyl group;

m is 0 or 1, provided that when m is 1, R^a is not an amino-substituted alkylcarbonylalkyl or amino-substituted alkylcarbonylaminoalkyl group, and when m

- 4 -

is 0, R^a is selected from an alkylaminocarbonylalkyl, cycloalkylaminocarbonylalkyl, heterocycloalkylaminocarbonylalkyl, arylaminocarbonylalkyl, heteroarylaminocarbonylalkyl and heteroarylcarbonylaminoalkyl group, provided that R^a is not substituted indolecarbonylaminoalkyl;

5 p is an integer of from 0 to 5;

A₁ is CH or N;

when p is 1, 2, 3, 4, or 5, A₂ is C(R^g)(R^h), N(Rⁱ), S, S(O), S(O)₂, or O, and when p is 0, A₂ is C(R^g)(R^h)(Rⁱ), N(R^g)(Rⁱ), S(R^g), S(O)(R^g), S(O)₂(R^g), or O(R^g), where each R^g, R^h and Rⁱ is independently H or a lower alkyl group;

10 each A₃ present is each independently C(R^g)(R^h), N(Rⁱ), S, S(O), S(O)₂, or O, where each R^g, R^h and Rⁱ is independently H or a lower alkyl group;

when p is 1, 2, 3, 4, or 5, A₄ is N(R^j), C(R^g)(R^h), or O, and when p is 0 (i.e., A₃ is not present), A₄ is N(R^j)(R^k), C(R^g)(R^h)(Rⁱ), and O(R^k), where each R^g, R^h and Rⁱ is independently H or a lower alkyl group, each R^j is H, an alkyl, aryl, or acyl group, and each R^k is H or an alkyl or aryl group;

15 provided that no more than two heteroatoms occur consecutively in the above-depicted ring formed by A₁, (A₂)_m, (A₃)_p, A₄, and C=O, where each dotted line in the ring depicts a single bond when A₂ is present (i.e., m = 1) and a hydrogen atom when A₂ is absent (i.e., m = 0); and

20 Z and Z¹ are each independently H, F, an alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group, where the alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group is unsubstituted or substituted with one or more suitable substituents, -C(O)R¹, -CO₂R¹, -CN, -C(O)NR¹R^m, -C(O)NR¹OR^m, -C(S)R¹, -C(S)OR¹, -C(S)NR¹R^m, -C(=NR¹)R^m, -C(=NR¹)OR^m, -NO₂, -SOR^m, -SO₂R¹, -SO₂NR¹R^m, -SO₂(NR¹)(OR^m), 25 -SONR¹, -SO₃R¹, -PO(OR¹)₂, -PO(OR¹)(OR^m), -PO(NR¹R^m)(ORⁿ), -PO(NR¹R^m)(NRⁿR^o), -C(O)NR¹NR^mRⁿ, -C(S)NR¹NR^mRⁿ, where R¹, R^m, Rⁿ and R^o are each independently H or an alkyl, cycloalkyl, aryl, heterocycloalkyl, acyl or thioacyl group, where the alkyl, cycloalkyl, aryl, heterocycloalkyl, acyl or thioacyl group is unsubstituted or substituted with one or more suitable substituents, or where any two of the R¹, R^m, Rⁿ and R^o, 30 taken together with the atoms to which they are bonded, form a heterocycloalkyl group, which may be optionally substituted,

- 5 -

or Z and R^d, together with the atoms to which they are bonded, form a cycloalkyl or heterocycloalkyl group, where Z and R^d are as defined above except for moieties that cannot form the cycloalkyl or heterocycloalkyl group,

5 or Z and Z¹, together with the atoms to which they are bonded, form a cycloalkyl or heterocycloalkyl group, where Z and Z¹ are as defined above (except for moieties that cannot form the cycloalkyl or heterocycloalkyl group);

or a prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate of said compound.

10 In another embodiment of the compounds of the above Formula I,

A₁ is CH or N;

A₂ is C(R^g)(R^h), N(Rⁱ), S, S(O), S(O)₂, or O, where each R^g, R^h and Rⁱ is independently H or a lower alkyl group;

each A₃ present is independently C(R^g)(R^h), N(Rⁱ), S, S(O), S(O)₂, or O, where each R^g, R^h and Rⁱ is independently H or a lower alkyl group;

15 when p is 1, 2, 3, 4, or 5, A₄ is N(R^j), C(R^g)(R^h), or O, and when p is 0, A₄ is N(R^j)(R^k), C(R^g)(R^h)(Rⁱ), and O(R^k), where each R^g, R^h and Rⁱ is independently H or a lower alkyl group, each R^j is H, an alkyl, aryl, or acyl group, and each R^k is H or an alkyl or aryl group;

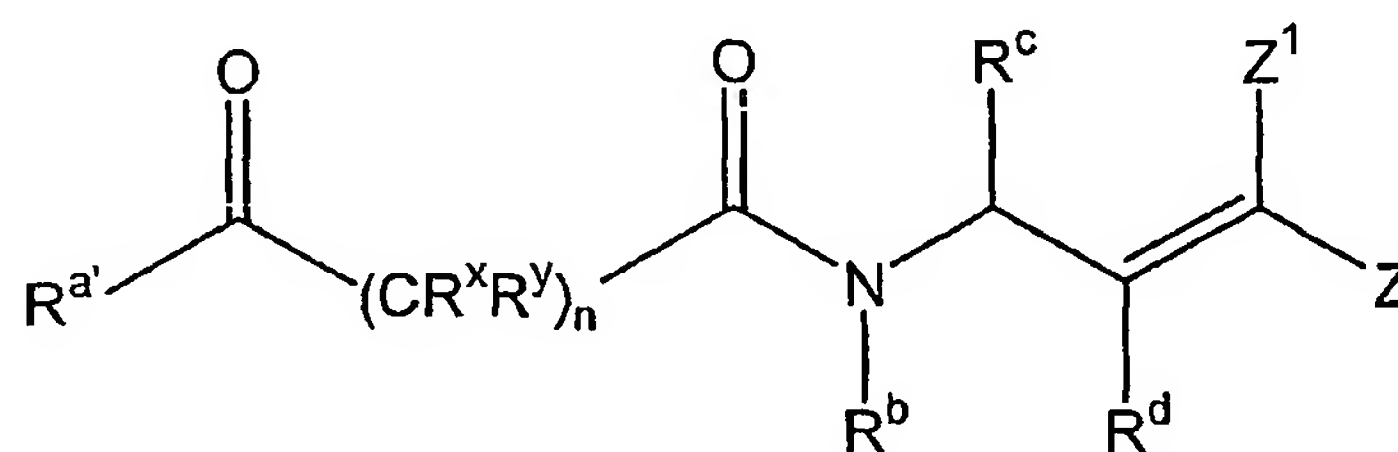
20 provided that no more than two heteroatoms occur consecutively in the above-depicted ring formed by A₁, (A₂)_m, (A₃)_p, A₄, and C=O, where each dotted line in the ring depicts a single bond when A₂ is present and a hydrogen atom when A₂ is absent; and

25 Z and Z¹ are each independently H, F, an alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group, where the alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group is unsubstituted or substituted with one or more suitable substituents, -C(O)R¹, -CO₂R¹, -CN, -C(O)NR¹R^m, -C(O)NR¹OR^m, -C(S)R¹, -C(S)NR¹R^m, -NO₂, -SOR^m, -SO₂R¹, -SO₂NR¹R^m, -SO₂(NR¹)(OR^m), -SONR¹, -SO₃R¹, -PO(OR¹)₂, -PO(OR¹)(OR^m), -PO(NR¹R^m)(ORⁿ), -PO(NR¹R^m)(NRⁿR^o), -C(O)NR¹NR^mRⁿ, -C(S)NR¹NR^mRⁿ, where R¹, R^m, Rⁿ and R^o are each independently H, an alkyl, 30 cycloalkyl, aryl, heterocycloalkyl, acyl or imoacyl group, where the alkyl, cycloalkyl, aaryl, heterocycloalkyl, acyl or thioacyl group is unsubstituted or substituted with one

- 6 -

or more suitable substituents, or where any two of the R^1 , R^m , R^n and R^o , taken together with the atoms to which they are bonded, form a heterocycloalkyl group, which is unsubstituted or substituted with one or more suitable substituents, or Z and Z^1 , together with the atoms to which they are bonded, form a cycloalkyl or heterocycloalkyl group, where Z and Z^1 are as defined above.

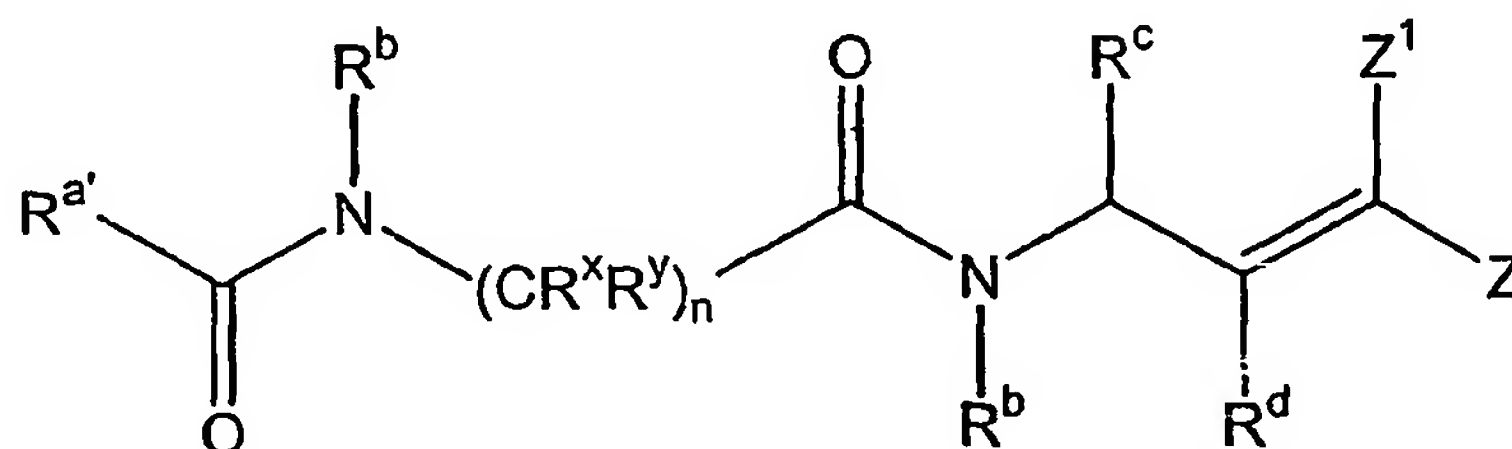
One embodiment of this invention relates to compounds useful for inhibiting the activity of picornaviral 3C proteases having the following general Formula II:



II

wherein $R^{a'}$ is an alkyl, cycloalkyl, aryl or heteroaryl group, where the alkyl, cycloalkyl, aryl or heteroaryl group is unsubstituted or substituted with one or more suitable substituents, n is 1, 2 or 3, m is 1, R^x and R^y are each independently selected from H and an alkyl group, unsubstituted or substituted with one or more suitable substituents, and R^b , R^c , R^d , Z and Z^1 are as defined above, provided that $R^{a'}$ is not an amino-substituted alkyl group.

Another embodiment of this invention relates to compounds useful for inhibiting the activity of picornaviral 3C proteases having the following general Formula III:

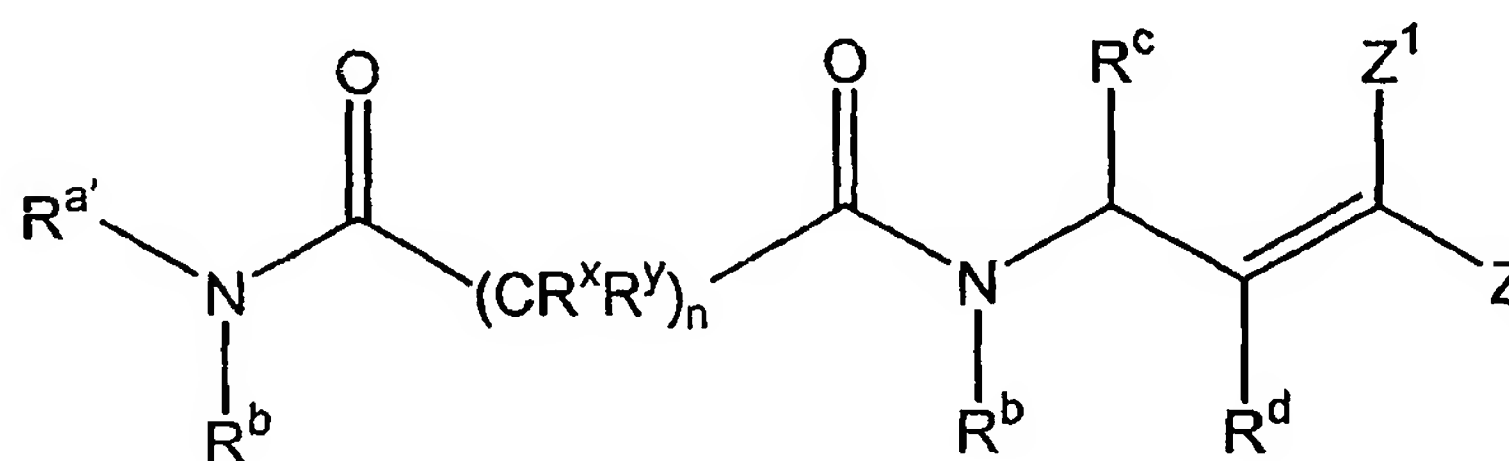


III

- 7 -

wherein R^a is an alkyl, cycloalkyl, aryl or heteroaryl group, where the alkyl, cycloalkyl, aryl or heteroaryl group is unsubstituted or substituted with one or more suitable substituents, n is 1, 2 or 3, m is 1, R^x and R^y are each independently selected from H and an alkyl group, unsubstituted or substituted with one or more suitable substituents, and R^b , R^c , R^d , Z and Z^1 are as defined above, provided that R^a is not an amino-substituted alkyl group.

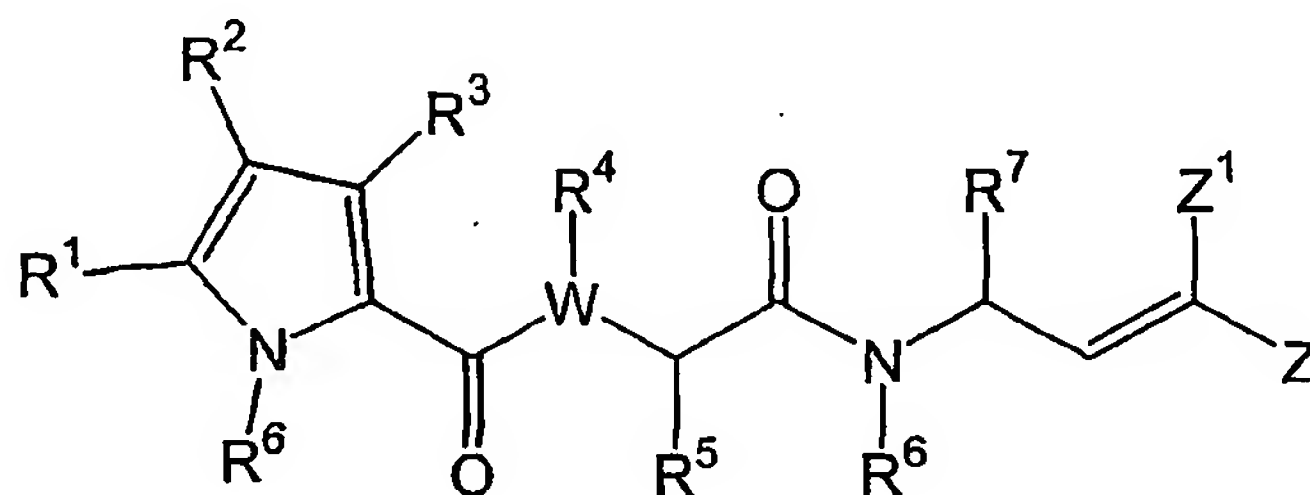
This invention also relates to compounds useful for inhibiting the activity of picornaviral 3C proteases having the following general Formula IV:



IV

wherein R^a is an alkyl, aryl, cycloalkyl, heterocycloalkyl or heteroaryl group, where the alkyl, aryl, cycloalkyl, heterocycloalkyl and heteroaryl group is unsubstituted or substituted with one or more suitable substituents, n is 1, 2 or 3, R^x and R^y are each independently selected from H and an alkyl group, unsubstituted or substituted with one or more suitable substituents, and R^b , R^c , R^d , Z and Z^1 are as defined above.

This invention relates to compounds useful for inhibiting the activity of picornaviral 3C proteases having the general Formula V:



V

- 8 -

wherein:

W is CH or N;

R¹ is H, halo or an alkoxy, alkyl, aryl, cycloalkyl, heterocycloalkyl or heteroaryl group, where the alkoxy, alkyl, aryl, cycloalkyl, heterocycloalkyl and heteroaryl group is unsubstituted or substituted with one or more suitable substituents;

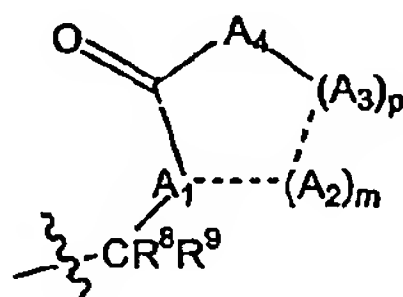
R² and R³ are each independently H, halo or an alkoxy or lower alkyl group, where the alkoxy or lower alkyl group is unsubstituted or substituted with a suitable substituent;

or R¹ together with R² form a cycloalkyl, heterocycloalkyl, aryl or heteroaryl ring, where the cycloalkyl, heterocycloalkyl, aryl or heteroaryl ring is unsubstituted or substituted with a suitable substituent;

R⁴ and R⁶ are each independently H or a lower alkyl group, unsubstituted or substituted with a suitable substituent;

R⁵ is H or an alkyl group, unsubstituted or substituted with a suitable substituent;

R⁷ is a moiety having the formula:



wherein:

R⁸ and R⁹ are each independently H or a lower alkyl group;

m is 0 or 1, provided that when W is N, m is 0 and R¹ together with R² form an aryl ring, the aryl ring is unsubstituted (e.g., R¹ together with R² and the pyrrole to which they are bound do not form a substituted indole);

p is an integer of from 0 to 5;

A₁ is CH or N;

when p is 1, 2, 3, 4, or 5, A₂ is C(R¹⁰)(R¹¹), N(R¹²), S, S(O), S(O)₂, or O, and when p is 0, A₂ is C(R¹⁰)(R¹¹)(R¹²), N(R¹⁰)(R¹²), S(R¹⁰), S(O)(R¹⁰), S(O)₂(R¹⁰), or O(R¹⁰) where each R¹⁰, R¹¹ and R¹² is independently H or a lower alkyl group;

each A₃ present is independently C(R¹⁰)(R¹¹), N(R¹²), S, S(O), S(O)₂, or O, where each R¹⁰, R¹¹ and R¹² is independently H or a lower alkyl group;

- 9 -

when p is 1, 2, 3, 4, or 5, A_4 is $N(R^{13})$, $C(R^{10})(R^{11})$, or O, and when p is 0, A_4 is $N(R^{13})(R^{14})$, $C(R^{10})(R^{11})(R^{12})$, and $O(R^{14})$, where each R^{10} , R^{11} and R^{12} is independently H or a lower alkyl group, each R^{13} is H or an alkyl, aryl, or acyl group, and each R^{14} is H or an alkyl or aryl group;

5 provided that no more than two heteroatoms occur consecutively in the above-depicted ring formed by A_1 , $(A_2)_m$, $(A_3)_p$, A_4 , and $C=O$, where each dotted line in the ring depicts a single bond when A_2 is present and a hydrogen atom when A_2 is absent; and

10 Z and Z^1 are each independently H, F, an alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group, where the alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group is unsubstituted or substituted with one or more suitable substituents, $-C(O)R^{15}$, $-CO_2R^{15}$, $-CN$, $-C(O)NR^{15}R^{16}$, $-C(O)NR^{15}OR^{16}$, $-C(S)R^{15}$, $-C(S)OR^{15}$, $-C(S)NR^{15}R^{16}$, $-C(=NR^{15})R^{16}$, $-C(=NR^{15})OR^{16}$, $-NO_2$, $-SOR^{16}$, $-SO_2R^{15}$, $-SO_2NR^{15}R^{16}$, $-SO_2(NR^{15})(OR^{16})$, $-SONR^{15}$, $-SO_3R^{15}$, $-PO(OR^{15})_2$, $-PO(OR^{15})(OR^{16})$,
 15 $-PO(NR^{15}R^{16})(OR^{17})$, $-PO(NR^{15}R^{16})(NR^{17}R^{18})$, $-C(O)NR^{15}NR^{16}R^{17}$, $-C(S)NR^{15}NR^{16}R^{17}$, where R^{15} , R^{16} , R^{17} and R^{18} are each independently H or an alkyl, cycloalkyl, aryl, heterocycloalkyl, acyl or thioacyl group, where the alkyl, cycloalkyl, aryl, heterocycloalkyl, acyl or thioacyl group is unsubstituted or substituted with one or more suitable substituents, or where any two of the R^{15} , R^{16} , R^{17} and R^{18} , taken together
 20 with the atoms to which they are bonded, form a heterocycloalkyl group, which is unsubstituted or substituted with one or more suitable substituents,

or Z and Z^1 , together with the atoms to which they are bonded, form a cycloalkyl or heterocycloalkyl group, where Z and Z^1 are as defined above (except for moieties that cannot form the cycloalkyl or heterocycloalkyl group).

25 In another embodiment of the compounds of Formula V,

A_1 is CH or N;

A_2 is $C(R^{10})(R^{11})$, $N(R^{12})$, S, S(O), S(O)₂, or O, where each R^{10} , R^{11} and R^{12} is independently H or a lower alkyl group;

each A_3 present is independently $C(R^{10})(R^{11})$, $N(R^{12})$, S, S(O), S(O)₂, or O,
 30 where each R^{10} , R^{11} and R^{12} is independently H or a lower alkyl group;

- 10 -

when p is 1, 2, 3, 4, or 5, A_4 is $N(R^{13})$, $C(R^{10})(R^{11})$, or O, and when p is 0, A_4 is $N(R^{13})(R^{14})$, $C(R^{10})(R^{11})(R^{12})$, and $O(R^{14})$, where each R^{10} , R^{11} and R^{12} is independently H or a lower alkyl group, each R^{13} is H or an alkyl, aryl, or acyl group, and each R^{14} is H or an alkyl or aryl group;

5 provided that no more than two heteroatoms occur consecutively in the above-depicted ring formed by A_1 , $(A_2)_m$, $(A_3)_p$, A_4 , and $C=O$, where each dotted line in the ring depicts a single bond when A_2 is present and a hydrogen atom when A_2 is absent; and

10 Z and Z^1 are each independently H, F, an alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group, where the alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group is unsubstituted or substituted with one or more suitable substituents, $-C(O)R^{15}$, $-CO_2R^{15}$, $-CN$, $-C(O)NR^{15}R^{16}$, $-C(O)NR^{15}OR^{16}$, $-C(S)R^{15}$, $-C(S)NR^{15}R^{16}$, $-NO_2$, $-SOR^{16}$, $-SO_2R^{15}$, $-SO_2NR^{15}R^{16}$, $-SO_2(NR^{15})(OR^{16})$, $-SONR^{15}$, $-SO_3R^{15}$, $-PO(OR^{15})_2$, $-PO(OR^{15})(OR^{16})$, $-PO(NR^{15}R^{16})(OR^{17})$,
 15 $-PO(NR^{15}R^{16})(NR^{17}R^{18})$, $-C(O)NR^{15}NR^{16}R^{17}$, $-C(S)NR^{15}NR^{16}R^{17}$, where R^{15} , R^{16} , R^{17} and R^{18} are each independently H or an alkyl, cycloalkyl, aryl, heterocycloalkyl, acyl or thioacyl group, where the alkyl, cycloalkyl, aryl, heterocycloalkyl, acyl or thioacyl group is unsubstituted or substituted with one or more suitable substituents, or where any two of the R^{15} , R^{16} , R^{17} and R^{18} , taken together with the atoms to which they are
 20 bonded, form a heterocycloalkyl group, which is unsubstituted or substituted with one or more suitable substituents, or Z and Z^1 , together with the atoms to which they are bonded, form a cycloalkyl or heterocycloalkyl group, where Z and Z^1 are as defined above.

In the compounds of the above-described Formulas I-V, R^c and R^7 are
 25 defined to provide structures where m is 1 and p is 1-5 (i.e., both A_2 and A_3 are present), m is 0 and p is 0 (i.e., both A_2 and A_3 are absent), m is 0 and p is 1-5 (i.e., A_2 is absent and A_3 is present) and m is 1 and p is 0 (i.e., A_2 is present and A_3 is absent). Accordingly, one of ordinary skill in the art will recognize that when both A_2 and A_3 are present (m is 1 and p is 1-5), the dotted line between A_1 and A_2 represents a bond and the dotted line between A_2 and A_3 represents a bond. When both A_2 and A_3 are
 30 absent (m is 0 and p is 0) A_2 , A_3 and the dotted line between these substituents are not


- 11 -

present and the remaining dotted line in the structure between A_1 and A_2 represents a hydrogen (e.g., A_1 is CH_2 or NH). In embodiments of this invention when A_2 is absent and A_3 is present (m is 0 and p is 1-5), the dotted line between A_1 and A_2 represents a hydrogen and the dotted line between A_2 and A_3 represents a hydrogen (e.g., A_1 is CH_2 or NH and A_3 is $\text{CH}(\text{R}^g)(\text{R}^h)$, $\text{NH}(\text{R}^i)$, SH , $\text{S}(\text{O})\text{H}$, $\text{S}(\text{O})_2\text{H}$, or OH or $\text{CH}(\text{R}^{10})(\text{R}^{11})$, $\text{NH}(\text{R}^{12})$, SH , $\text{S}(\text{O})\text{H}$, $\text{S}(\text{O})_2\text{H}$, or OH); and when A_2 is present and A_3 is absent (m is 1 and p is 0), the dotted line between A_1 and A_2 represents a bond and A_2 is $\text{C}(\text{R}^g)(\text{R}^h)(\text{R}^i)$, $\text{N}(\text{R}^g)(\text{R}^i)$, $\text{S}(\text{R}^g)$, $\text{S}(\text{O})(\text{R}^g)$, $\text{S}(\text{O})_2(\text{R}^g)$, or $\text{O}(\text{R}^g)$ or A_2 is $\text{C}(\text{R}^{10})(\text{R}^{11})(\text{R}^{12})$, $\text{N}(\text{R}^{10})(\text{R}^{12})$, $\text{S}(\text{R}^{10})$, $\text{S}(\text{O})(\text{R}^{10})$, $\text{S}(\text{O})_2(\text{R}^{10})$, or $\text{O}(\text{R}^{10})$ or the dotted line between A_2 and A_3 represents a hydrogen and A_2 is $\text{CH}(\text{R}^g)(\text{R}^h)$, $\text{NH}(\text{R}^i)$, SH , $\text{S}(\text{O})\text{H}$, $\text{S}(\text{O})_2\text{H}$, or OH or A_2 is $\text{CH}(\text{R}^{10})(\text{R}^{11})$, $\text{NH}(\text{R}^{12})$, SH , $\text{S}(\text{O})\text{H}$, $\text{S}(\text{O})_2\text{H}$, or OH . In preferred embodiments of the compounds of Formula I-V of this invention, m is 1 and p is 1 or 2 or m is 0 and p is 0 or m is 1 and p is 0. More preferably, when m is 1 and p is 1 or 2, A_2 and A_3 are both $\text{C}(\text{R}^g)(\text{R}^h)$ or $\text{C}(\text{R}^{10})(\text{R}^{11})$, respectively. More preferably, m is 1 and p is 1.

In addition to compounds of the Formulas I-V, antipicornaviral agents of the invention include prodrugs, pharmaceutically active metabolites, and pharmaceutically acceptable salts and solvates of such compounds.

20

DETAILED DESCRIPTION OF INVENTION

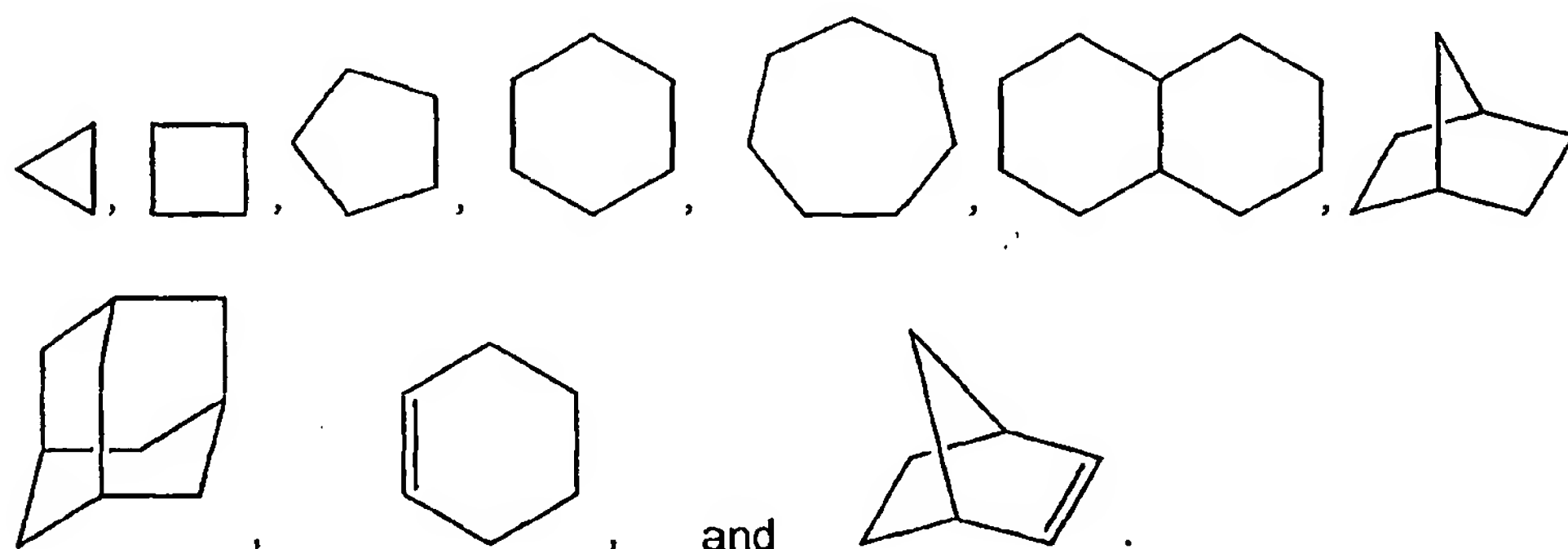
In accordance with a convention used in the art,  is used in structural formulas herein to depict the bond that is the point of attachment of the moiety or substituent to the core or backbone structure.

25

As used herein, the term "alkyl" represents a straight- or branched-chain saturated or unsaturated hydrocarbon, containing 1 to 10 carbon atoms which may be unsubstituted or substituted by one or more of the substituents described below. A C_1 - C_6 alkyl represents an alkyl substituent containing 1 to 6 carbon atoms. Exemplary alkyl substituents include, but are not limited to methyl (Me), ethyl (Et), propyl, isopropyl, butyl, isobutyl, t-butyl, ethenyl, propenyl, butenyl, pentenyl, ethynyl,

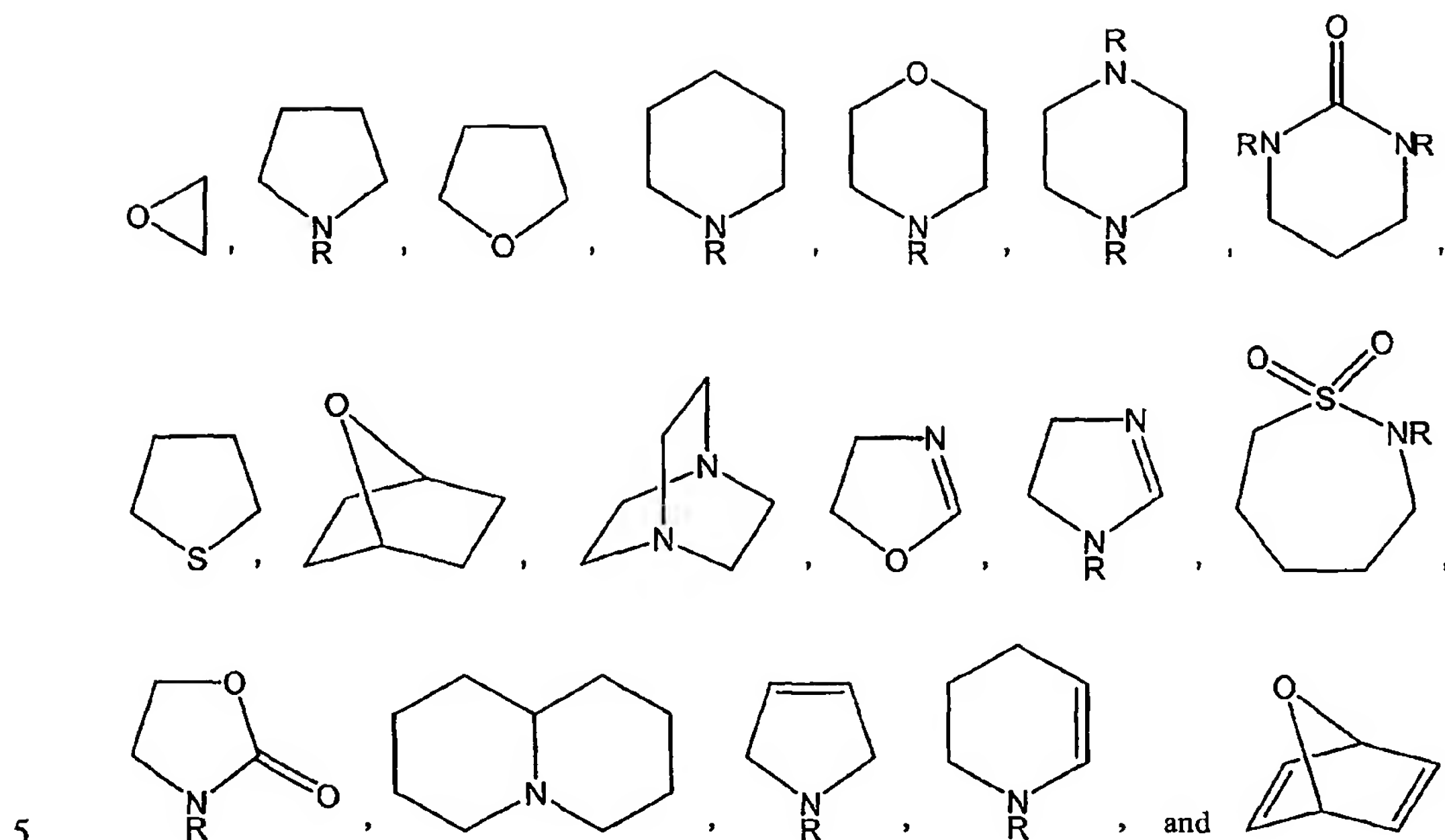
butynyl, propynyl (propargyl, isopropynyl), pentynyl, hexynyl and the like. The term "lower alkyl" refers to an alkyl group containing from 1 to 4 carbon atoms.

"Cycloalkyl" represents a group comprising a non-aromatic monocyclic, bicyclic, or tricyclic hydrocarbon containing from 3 to 14 carbon atoms which may be unsubstituted or substituted by one or more of the substituents described below and may be saturated or unsaturated. Exemplary cycloalkyls include monocyclic rings having from 3-7, preferably 3-6, carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like, that may be fully saturated or partially unsaturated. Illustrative examples of cycloalkyl groups include the following:

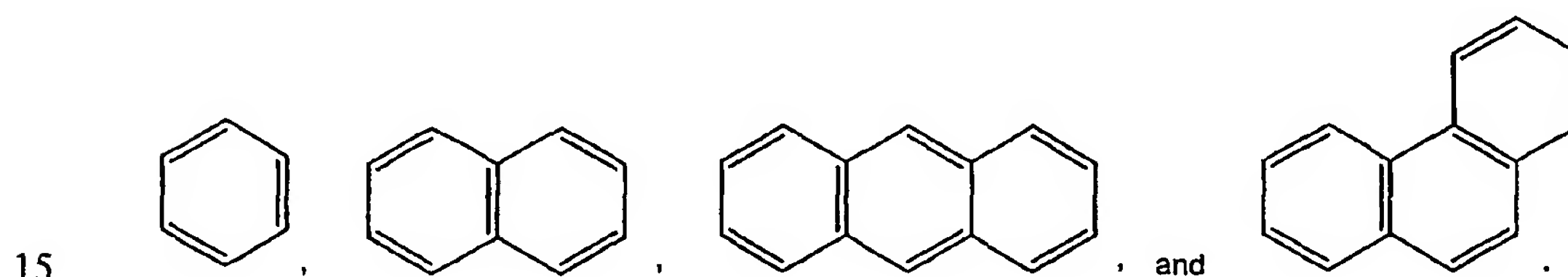


"Heterocycloalkyl" represents a group comprising a non-aromatic, monovalent monocyclic, bicyclic, or tricyclic radical, which is saturated or partially unsaturated, containing 3 to 18 ring atoms, which includes 1 to 5 heteroatoms selected from nitrogen, oxygen and sulfur, and which may be unsubstituted or substituted by one or more of the substituents described below. Illustrative examples of heterocycloalkyl groups include, but are not limited to, azetidiny, pyrrolidyl, piperidyl, piperazinyl, morpholinyl, tetrahydro-2H-1,4-thiazinyl, tetrahydrofuryl, dihydrofuryl, tetrahydropyranyl, dihydropyranyl, 1,3-dioxolanyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-oxathiolanyl, 1,3-oxathianyl, 1,3-dithianyl, azabicyclo[3.2.1]octyl, azabicyclo[3.3.1]nonyl, azabicyclo[4.3.0]nonyl, oxabicyclo[2.2.1]heptyl, 1,5,9-triazacyclododecyl, and the like. Illustrative examples of heterocycloalkyl groups include the following moieties:

- 13 -

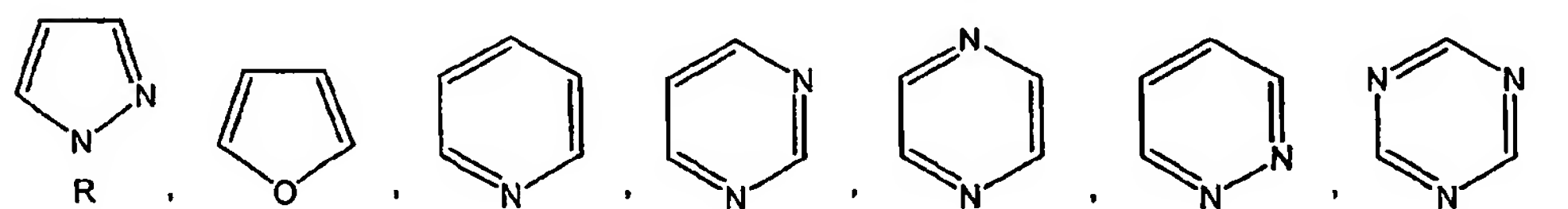
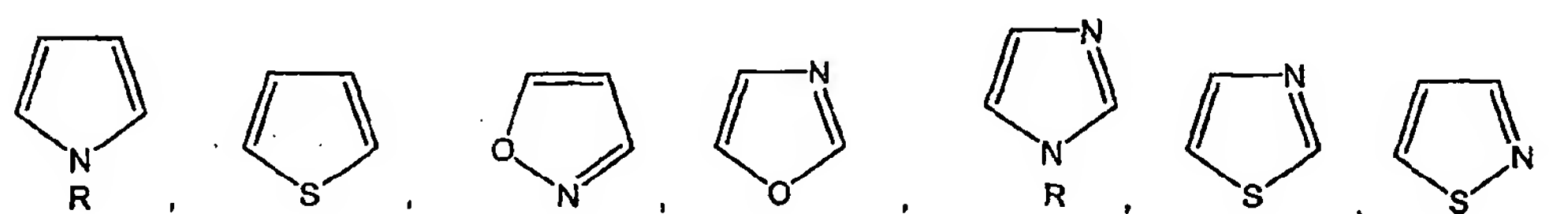


"Aryl" represents a group comprising an aromatic, monovalent monocyclic, bicyclic, or tricyclic radical containing from 6 to 18 carbon ring atoms, which may be unsubstituted or substituted by one or more of the substituents described below, and to which may be fused one or more cycloalkyl groups, heterocycloalkyl groups or heteroaryl groups, which themselves may be unsubstituted or substituted by one or more suitable substituents. Illustrative examples of aryl groups include the following moieties:

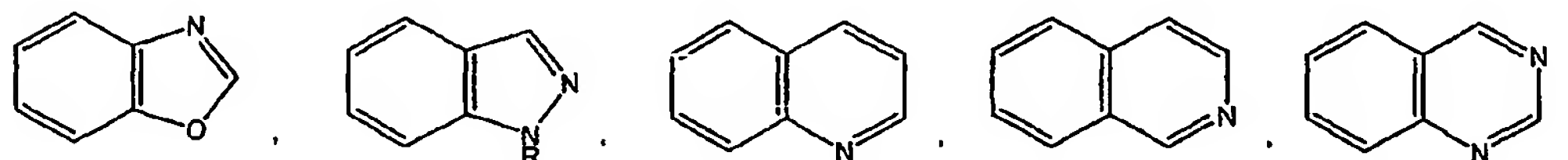
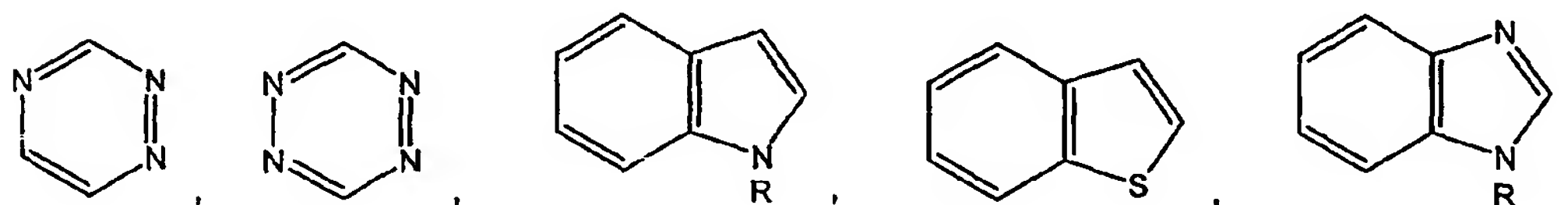


than one N-oxide derivative may be formed) of the nitrogen-containing heteroaryl groups described herein. Illustrative examples of heteroaryl groups include, but are not limited to, thienyl, pyrrolyl, imidazolyl, pyrazolyl, furyl, isothiazolyl, furazanyl, isoxazolyl, thiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, benzo[b]thienyl, naphtho[2,3-b]thianthrenyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathienyl, indoliziny, isoindolyl, indolyl, indazolyl, purinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinoxalyl, quinzolyl, benzothiazolyl, benzimidazolyl, tetrahydroquinolyl, cinnolyl, pteridinyl, carbazolyl, beta-carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, phenazinyl, isothiazolyl, phenothiazinyl, and phenoxazinyl. Illustrative examples of N-oxide derivatives of heteroaryl groups include, but are not limited to, pyridyl N-oxide, pyrazinyl N-oxide, pyrimidinyl N-oxide, pyridazinyl N-oxide, triazinyl N-oxide, isoquinolyl N-oxide, and quinolyl N-oxide. Further examples of heteroaryl groups include the following moieties:

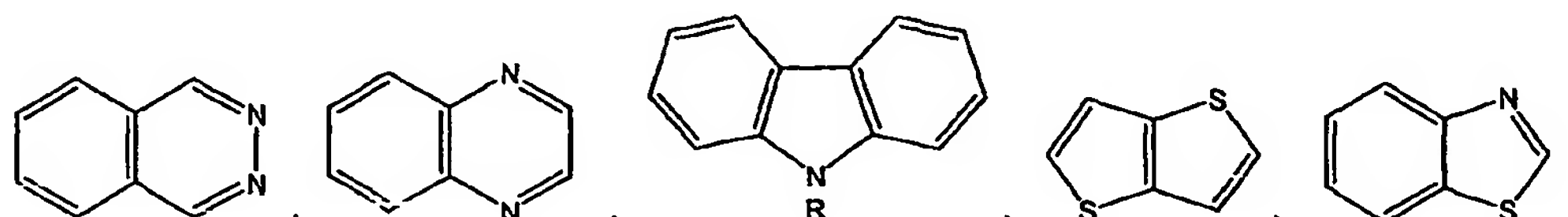
15

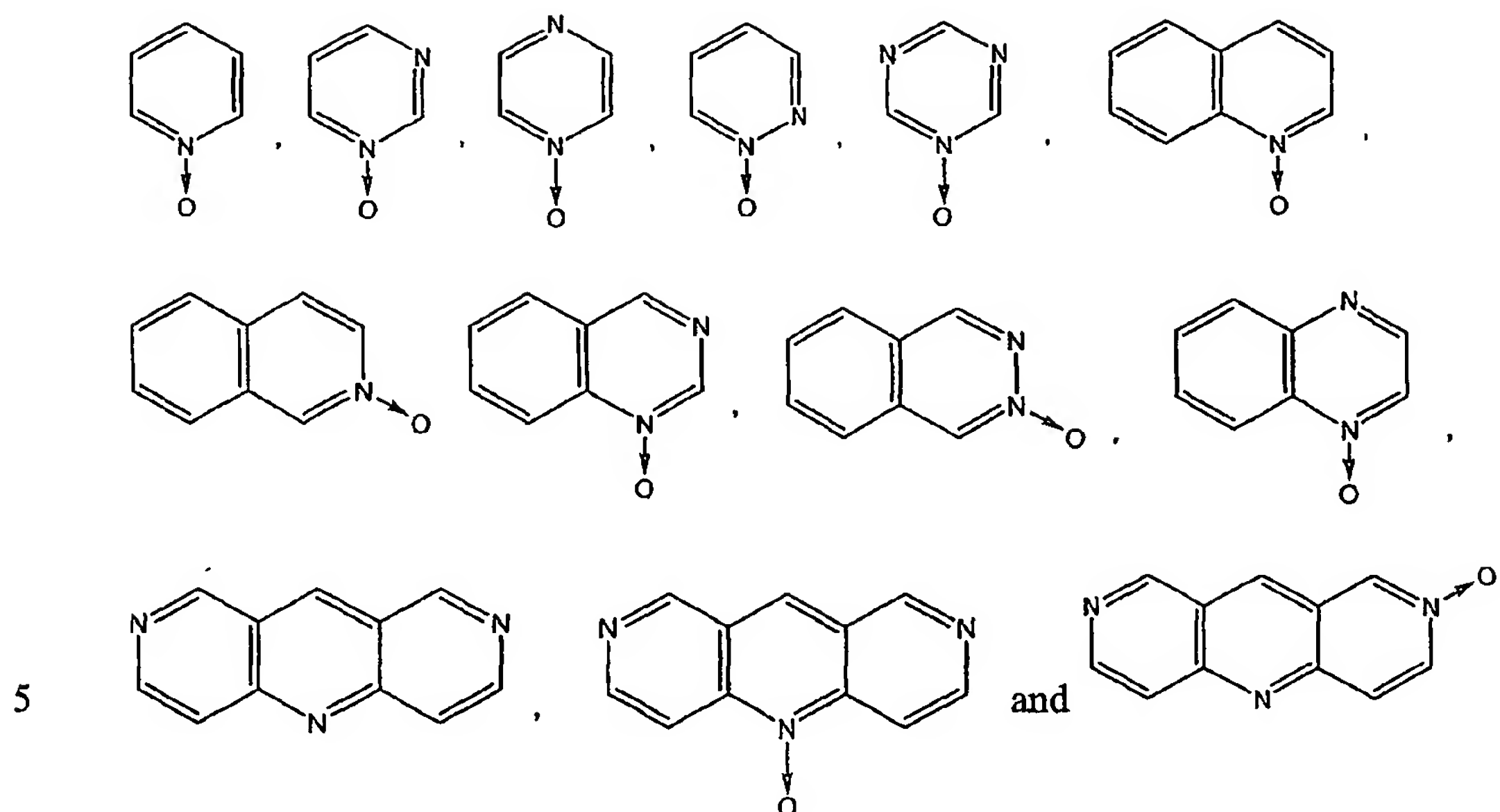


20



25





wherein R is H, alkyl or hydroxyl.

The term "suitable substituent" represents a substituent that is optionally present on any of the above alkyl, aryl, cycloalkyl, heterocycloalkyl or heteroaryl groups, described herein, and is selected from alkyl (except for alkyl) haloalkyl, haloaryl, halocycloalkyl, haloheterocycloalkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, nitro, amino, hydroxamino, cyano, halo, hydroxyl, alkoxy, alkylenedioxy, aryloxy, cycloalkoxy, heterocycloalkoxy, heteroaryloxy, alkylcarbonyl, alkylloxycarbonyl, alkylcarbonyloxy, arylcarbonyl, arylcarbonyloxy, aryloxycarbonyl, cycloalkylcarbonyl, cycloalkylcarbonyloxy, cycloalkyloxycarbonyl, heteroarylcarbonyl, heteroarylcarbonyloxy, heteroaryloxycarbonyl, heterocycloalkylcarbonyl, heterocycloalkylcarbonyloxy, heterocycloalkyloxycarbonyl, carboxyl, carbamoyl, formyl, keto (oxo), thioketo, sulfo, alkylamino, cycloalkylamino, arylamino, heterocycloalkylamino, heteroarylamino, dialkylamino, alkylaminocarbonyl, cycloalkylaminocarbonyl, arylaminocarbonyl, heterocycloalkylaminocarbonyl, heteroarylaminocarbonyl, dialkylaminocarbonyl, alkylaminothiocarbonyl, cycloalkylaminothiocarbonyl, arylaminothiocarbonyl, heterocycloalkylaminothiocarbonyl, heteroarylaminothiocarbonyl, dialkylaminothiocarbonyl, alkylsulfonyl, arylsulfonyl, alkylsulfenyl, arylsulfenyl, alkylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, heterocycloalkylcarbonylamino, heteroarylcarbonylamino, alkylthiocarbonylamino,

- 16 -

cycloalkylthiocarbonylamino, arylthiocarbonylamino, heterocycloalkylthiocarbonylamino, heteroarylthiocarbonylamino, alkylsulfonyloxy, arylsulfonyloxy, alkylsulfonylamino, arylsulfonylamino, mercapto, alkylthio, arylthio, and heteroarylthio groups, where any of the alkyl, alkylene, aryl, cycloalkyl, heterocycloalkyl, heteroaryl moieties present in the above substituents may be further substituted with one or more substituents selected from nitro, amino, cyano, halo, haloalkyl, haloaryl, hydroxyl, keto, hydroxamino, alkylamino, dialkylamino, mercapto, and unsubstituted alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, alkoxy, aryloxy, alkylthio or arylthio groups and where any of the aryl or heteroaryl moieties may be substituted with alkylenedioxy. Preferred "suitable substituents" include alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, halo, hydroxyl, alkoxy, alkylenedioxy, aryloxy, cycloalkoxy, heteroaryloxy, and carboxyl. The alkyl, alkylene, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl moieties of any of the above substituents may be optionally substituted by one or more of alkyl (except for alkyl), halo, haloalkyl, aryl or heteroaryl, where the aryl or heteroaryl is unsubstituted or substituted with one or more substituents, (e.g., haloaryl), independently selected from alkyl, haloalkyl, alkylenedioxy, nitro, amino, hydroxamino, alkylamino, dialkylamino, halo, hydroxyl, alkoxy, haloalkoxy, aryloxy, mercapto, alkylthio or arylthio groups.

The terms "halogen" and "halo" represent chloro, fluoro, bromo or iodo substituents. "Heterocycle" is intended to mean a heteroaryl or heterocycloalkyl group. "Acyl" is intended to mean a $-C(O)-R$ radical, wherein R is an alkyl, cycloalkyl, aryl, heterocycloalkyl or heteroaryl group. "Acyloxy" is intended to mean an $-OC(O)-R$ radical, wherein R is an alkyl, cycloalkyl, aryl, heterocycloalkyl or heteroaryl group. "Thioacyl" is intended to mean a $-C(S)-R$ radical, wherein R is an alkyl, cycloalkyl, aryl, heterocycloalkyl or heteroaryl group. "Sulfonyl" is intended to mean an $-SO_2-$ biradical. "Sulfenyl" is intended to mean an $-SO-$ biradical. "Sulfo" is intended to mean an $-SO_2H$ radical. Sulfoxide is intended to mean a $-SO_3^-$ radical. "Hydroxy" is intended to mean the radical $-OH$. "Amine" or "amino" is intended to mean the radical $-NH_2$. "Alkylamino" is intended to mean the radical $-NHR_a$, wherein R_a is an alkyl group. "Dialkylamino" is intended to mean the radical $-NR_aR_b$, wherein R_a and R_b are each independently an alkyl group, and is intended to include

- 17 -

heterocycloalkyl groups, wherein R_a and R_b , taken together, form a heterocyclic ring that includes the amine nitrogen. "Hydroxamino" is intended to mean the radical -N-OH. "Alkoxy" is intended to mean the radical -OR_a, wherein R_a is an alkyl group. Exemplary alkoxy groups include methoxy, ethoxy, propoxy, and the like. "Lower alkoxy" groups have alkyl moieties having from 1 to 4 carbons. "Alkylenedioxy" is intended to mean the divalent radical -OR_aO- which is bonded to adjacent atoms on an aryl or heteroaryl moiety (e.g., adjacent atoms on a phenyl or naphthyl ring), wherein R_a is a lower alkyl group. "Alkoxycarbonyl" is intended to mean the radical -C(O)OR_a, wherein R_a is an alkyl group. "Alkylsulfonyl" is intended to mean the radical -SO₂R_a, wherein R_a is an alkyl group. "Alkylaminocarbonyl" is intended to mean the radical -C(O)NHR_a, wherein R_a is an alkyl group. "Dialkylaminocarbonyl" is intended to mean the radical -C(O)NR_aR_b, wherein R_a and R_b are each independently an alkyl group. "Mercapto" is intended to mean the radical -SH. "Alkylthio" is intended to mean the radical -SR_a, wherein R_a is an alkyl group. "Carboxyl" is intended to mean the radical -C(O)OH. "Keto" or "oxo" is intended to mean the radical =O. "Thioketo" is intended to mean the radical =S. "Carbamoyl" is intended to mean the radical -C(O)NH₂. "Cycloalkylalkyl" is intended to mean the radical -alkyl-cycloalkyl, wherein alkyl and cycloalkyl are defined as above, and is exemplified by the bonding arrangement present in the groups -CH₂-cyclohexane or -CH₂-cyclohexene. "Arylalkyl" is intended to mean the radical -alkylaryl, wherein alkyl and aryl are defined as above, and is exemplified by the bonding arrangement present in a benzyl group. "Aminocarbonylalkyl" is intended to mean the radical -alkylC(O)NH₂ and is exemplified by the bonding arrangement present in the group -CH₂CH₂C(O)NH₂. "Alkylaminocarbonylalkyl" is intended to mean the radical -alkylC(O)NHR_a, wherein R_a is an alkyl group and is exemplified by the bonding arrangement present in the group -CH₂CH₂C(O)NHCH₃. "Alkylcarbonylaminoalkyl" is intended to mean the radical -alkylNHC(O)-alkyl and is exemplified by the bonding arrangement present in the group -CH₂NHC(O)CH₃. "Dialkylaminocarbonylalkyl" is intended to mean the radical -alkylC(O)NR_aR_b, wherein R_a and R_b are each independently an alkyl group. "Aryloxy" is intended to mean the radical -OR_c, wherein R_c is an aryl group. "Heteroaryloxy" is intended to mean the radical -OR_d,

- 18 -

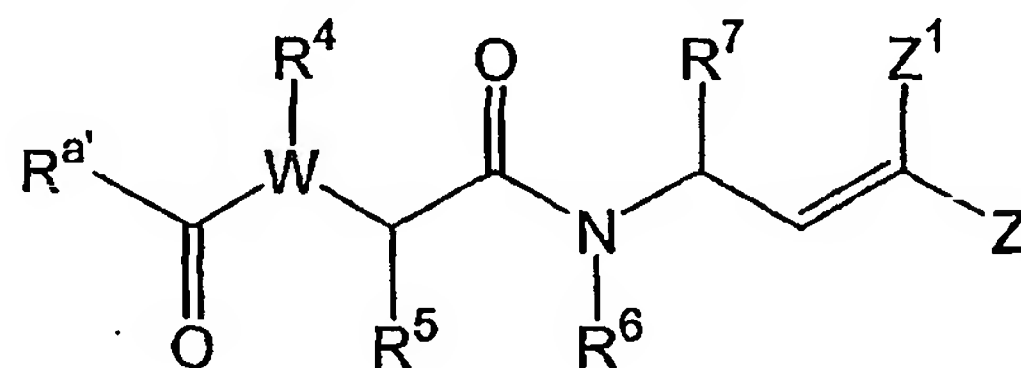
wherein R_d is a heteroaryl group. "Arylthio" is intended to mean the radical $-SR_c$, wherein R_c is an aryl group. "Heteroarylthio" is intended to mean the radical $-SR_d$, wherein R_d is a heteroaryl group.

5 The alkyl, cycloalkyl, aryl, heterocycloalkyl and heteroaryl groups and the substituents containing these groups, as defined hereinabove, may be optionally substituted by at least one other substituent. The term "optionally substituted" is intended to expressly indicate that the specified group is unsubstituted or substituted by one or more suitable substituents. Various groups may be unsubstituted or substituted (i.e., they are optionally substituted) as indicated.

10 If the substituents themselves are not compatible with the synthetic methods of this invention, the substituent may be protected with a suitable protecting group that is stable to the reaction conditions used in these methods. The protecting group may be removed at a suitable point in the reaction sequence of the method to provide a desired intermediate or target compound. Suitable protecting groups and the methods
15 for protecting and de-protecting different substituents using such suitable protecting groups are well known to those skilled in the art; examples of which may be found in T. Greene and P. Wuts, Protecting Groups in Chemical Synthesis (3rd ed.), John Wiley & Sons, NY (1999), which is incorporated herein by reference in its entirety. In some instances, a substituent may be specifically selected to be reactive under the reaction
20 conditions used in the methods of this invention. Under these circumstances, the reaction conditions convert the selected substituent into another substituent that is either useful in an intermediate compound in the methods of this invention or is a desired substituent in a target compound.

- 19 -

Particular embodiments of this invention comprise the compounds of Formulas II and III, wherein n is 2 or 1, respectively, depicted by the formula:



VI

wherein:

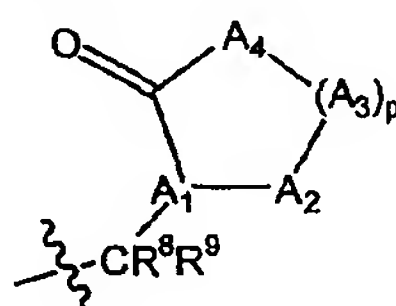
W is CH or N;

R^{a'} is an alkyl, cycloalkyl, aryl or heteroaryl group, where the alkyl, cycloalkyl, aryl, and heteroaryl group is unsubstituted or substituted with one or more suitable substituents, provided that R^{a'} is not an amino-substituted alkyl group;

R⁴ and R⁶ are each independently H or a lower alkyl group;

R⁵ is H or an alkyl group;

R⁷ is a substituent having the formula:



wherein:

R⁸ and R⁹ are each independently H or lower alkyl;

p is an integer of from 1 to 5;

A₁ is CH or N;

when p is 1, 2, 3, 4, or 5, A₂ is C(R¹⁰)(R¹¹), N(R¹²), S, S(O), S(O)₂, or O, and when p is 0, A₂ is C(R¹⁰)(R¹¹)(R¹²), N(R¹⁰)(R¹²), S(R¹⁰), S(O)(R¹⁰), S(O)₂(R¹⁰), or O(R¹⁰) where each R¹⁰, R¹¹ and R¹² is independently H or a lower alkyl group;

each A₃ present is independently C(R¹⁰)(R¹¹), N(R¹²), S, S(O), S(O)₂, or O, where each R¹⁰, R¹¹ and R¹² is independently H or a lower alkyl group;

when p is 1, 2, 3, 4, or 5, A₄ is N(R¹³), C(R¹⁰)(R¹¹), or O, and when p is 0, A₄ is N(R¹³)(R¹⁴), C(R¹⁰)(R¹¹)(R¹²), and O(R¹⁴), where each R¹⁰, R¹¹ and R¹² is independently H or a lower alkyl group, each R¹³ is H or an alkyl, aryl, or acyl group, and each R¹⁴ is H or an alkyl or aryl group;

- 20 -

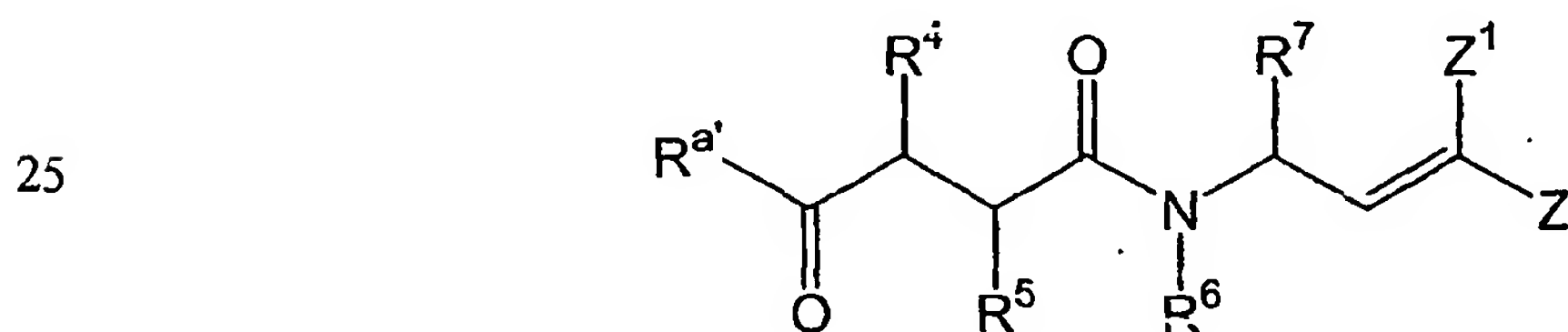
provided that no more than two heteroatoms occur consecutively in the above-depicted ring formed by A_1 , $(A_2)_m$, $(A_3)_p$, A_4 , and $C=O$, where each dotted line in the ring depicts a single bond when A_2 is present and a hydrogen atom when A_2 is absent; and

5 Z and Z^1 are each independently H, F, an alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group, where the alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group is unsubstituted or substituted with one or more suitable substituents, $-C(O)R^{15}$, $-CO_2R^{15}$, $-CN$, $-C(O)NR^{15}R^{16}$, $-C(O)NR^{15}OR^{16}$, $-C(S)R^{15}$, $-C(S)OR^{15}$, $-C(S)NR^{15}R^{16}$, $-C(=NR^{15})R^{16}$, $-C(=NR^{15})OR^{16}$, $-NO_2$, $-SOR^{16}$, $-SO_2R^{15}$, $-SO_2NR^{15}R^{16}$,
 10 $-SO_2(NR^{15})(OR^{16})$, $-SONR^{15}$, $-SO_3R^{15}$, $-PO(OR^{15})_2$, $-PO(OR^{15})(OR^{16})$, $-PO(NR^{15}R^{16})(OR^{17})$, $-PO(NR^{15}R^{16})(NR^{17}R^{18})$, $-C(O)NR^{15}NR^{16}R^{17}$, $-C(S)NR^{15}NR^{16}R^{17}$, where R^{15} , R^{16} , R^{17} and R^{18} are each independently H or an alkyl, cycloalkyl, aryl, heterocycloalkyl, acyl or thioacyl group, where the alkyl, cycloalkyl, aryl, heterocycloalkyl, acyl or thioacyl group is unsubstituted or substituted with one or
 15 more suitable substituents, or where any two of the R^{15} , R^{16} , R^{17} and R^{18} , taken together with the atoms to which they are bonded, form a heterocycloalkyl group, which is unsubstituted or substituted with one or more suitable substituents,

 or Z and Z^1 , together with the atoms to which they are bonded, form a cycloalkyl or heterocycloalkyl group, where Z and Z^1 are as defined above (except for
 20 moieties that cannot form the cycloalkyl or heterocycloalkyl group);

 or a prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate thereof of said compound.

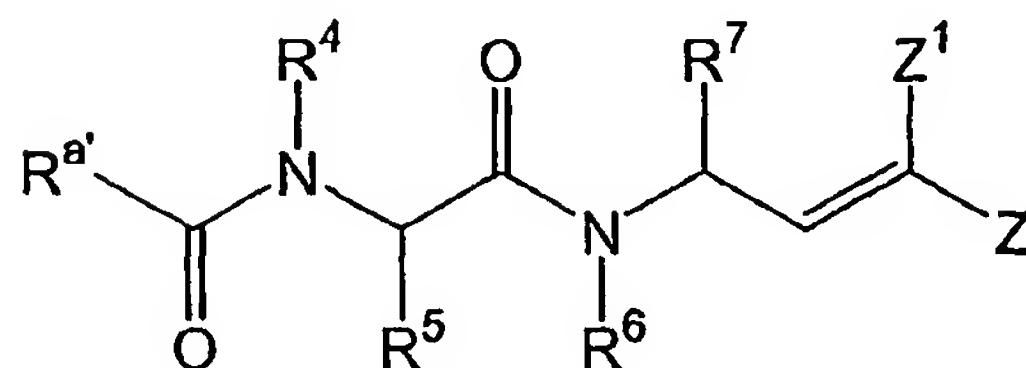
More specifically, preferred embodiments of Formula VI of this invention comprise the compounds depicted by the formula:



VII

- 21 -

wherein R^a , R^4 , R^5 , R^6 , R^7 , Z and Z^1 are as defined above; and the compounds depicted by the formula:

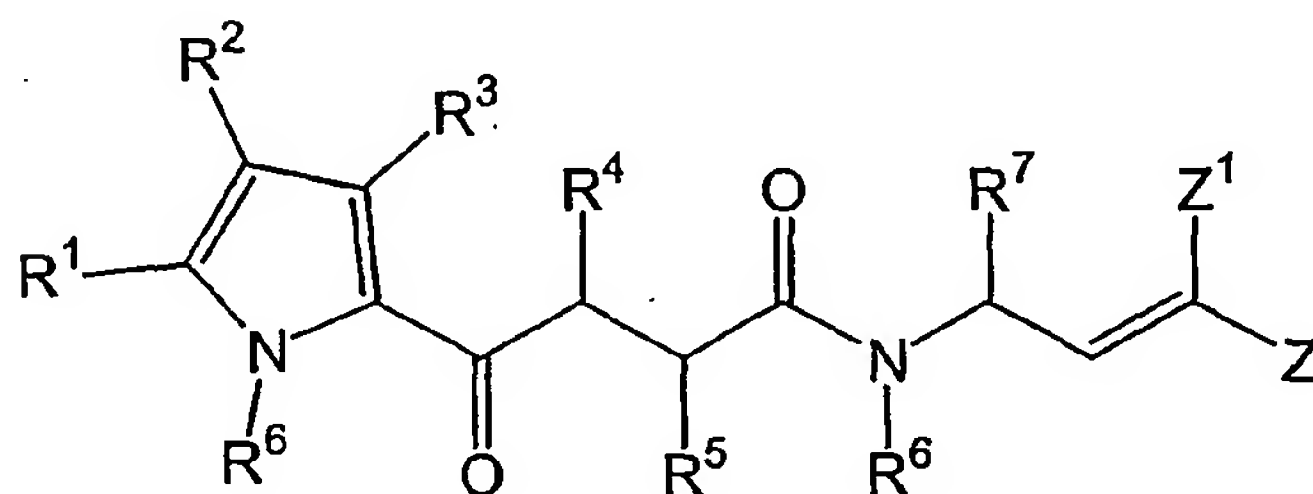


5

VIII

wherein R^a , R^4 , R^5 , R^6 , R^7 , Z and Z^1 are as defined above.

In particular, this invention comprises the compounds depicted by the formula:



10

IX

wherein:

R^1 is H, halo or an alkoxy, alkyl, aryl, cycloalkyl, heterocycloalkyl or heteroaryl group, where the alkoxy, alkyl, aryl, cycloalkyl, heterocycloalkyl, or heteroaryl group is unsubstituted or substituted with one or more suitable substituents;

15

R^2 and R^3 are each independently H, halo or an alkoxy or lower alkyl group, where the alkoxy or lower alkyl group is unsubstituted or substituted with one or more suitable substituents;

20

or R^1 together with R^2 form a cycloalkyl, heterocycloalkyl, aryl or heteroaryl ring, where the cycloalkyl, heterocycloalkyl, aryl or heteroaryl ring is unsubstituted or substituted with one or more suitable substituents;

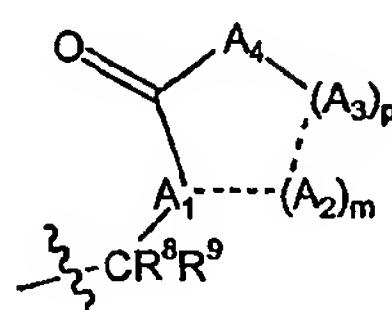
R^4 and R^6 are each independently H or a lower alkyl group, unsubstituted or substituted with one or more suitable substituents;

25

R^5 is H or an alkyl group, unsubstituted or substituted with one or more suitable substituents;

- 22 -

R^7 is a moiety having the formula:



wherein:

R^8 and R^9 are each each independently H or a lower alkyl group;

5 m is 0 or 1;

p is an integer of from 0 to 5;

A_1 is CH or N;

when p is 1, 2, 3, 4, or 5, A_2 is $C(R^{10})(R^{11})$, $N(R^{12})$, S, $S(O)$, $S(O)_2$, or O, and

10 when p is 0, A_2 is $C(R^{10})(R^{11})(R^{12})$, $N(R^{10})(R^{12})$, $S(R^{10})$, $S(O)(R^{10})$, $S(O)_2(R^{10})$, or $O(R^{10})$ where each R^{10} , R^{11} and R^{12} is independently H or a lower alkyl group;

each A_3 present is independently $C(R^{10})(R^{11})$, $N(R^{12})$, S, $S(O)$, $S(O)_2$, or O, where each R^{10} , R^{11} and R^{12} is independently H or a lower alkyl group;

15 when p is 1, 2, 3, 4, or 5, A_4 is $N(R^{13})$, $C(R^{10})(R^{11})$, or O, and when p is 0, A_4 is $N(R^{13})(R^{14})$, $C(R^{10})(R^{11})(R^{12})$, and $O(R^{14})$, where each R^{10} , R^{11} and R^{12} is independently H or a lower alkyl group, each R^{13} is H or an alkyl, aryl, or acyl group, and each R^{14} is H or an alkyl or aryl group;

20 provided that no more than two heteroatoms occur consecutively in the above-depicted ring formed by A_1 , $(A_2)_m$, $(A_3)_p$, A_4 , and $C=O$, where each dotted line in the ring depicts a single bond when A_2 is present and a hydrogen atom when A_2 is absent; and

Z and Z^1 are each independently H, F, an alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group, where the alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group is unsubstituted or substituted with one or more suitable substituents, $-C(O)R^{15}$, $-CO_2R^{15}$, $-CN$, $-C(O)NR^{15}R^{16}$, $-C(O)NR^{15}OR^{16}$, $-C(S)R^{15}$, $-C(S)OR^{15}$, $-C(S)NR^{15}R^{16}$, $-C(=NR^{15})R^{16}$, $-C(=NR^{15})OR^{16}$, $-NO_2$, $-SOR^{16}$, $-SO_2R^{15}$, $-SO_2NR^{15}R^{16}$, $-SO_2(NR^{15})(OR^{16})$, $-SONR^{15}$, $-SO_3R^{15}$, $-PO(OR^{15})_2$, $-PO(OR^{15})(OR^{16})$, $-PO(NR^{15}R^{16})(OR^{17})$, $-PO(NR^{15}R^{16})(NR^{17}R^{18})$, $-C(O)NR^{15}NR^{16}R^{17}$, $-C(S)NR^{15}NR^{16}R^{17}$, where R^{15} , R^{16} , R^{17} and R^{18} are each independently H or an alkyl, cycloalkyl, aryl, heterocycloalkyl, acyl or thioacyl group, where the alkyl, cycloalkyl, aryl,

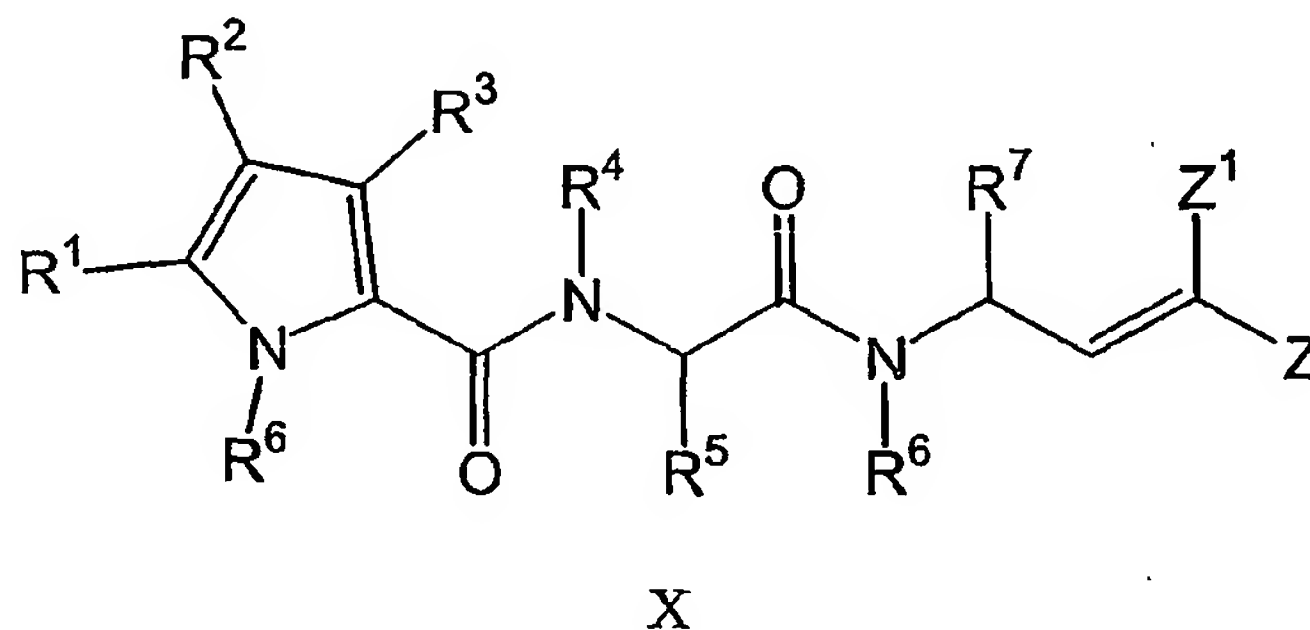
- 23 -

heterocycloalkyl, acyl or thioacyl group is unsubstituted or substituted with one or more suitable substituents, or where any two of the R^{15} , R^{16} , R^{17} and R^{18} , taken together with the atoms to which they are bonded, form a heterocycloalkyl group, which is unsubstituted or substituted with one or more suitable substituents,

5 or Z and Z^1 , together with the atoms to which they are bonded, form a cycloalkyl or heterocycloalkyl group, where Z and Z^1 are as defined above (except for moieties that cannot form the cycloalkyl or heterocycloalkyl group);

or a prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate of said compound.

10 Another embodiment of this invention comprises the compounds depicted by the formula:



15 wherein:

R^1 is H, halo or an alkoxy, alkyl, aryl, cycloalkyl, heterocycloalkyl, or heteroaryl group, where the alkoxy, alkyl, aryl, cycloalkyl, heterocycloalkyl, or heteroaryl group is unsubstituted or substituted with one or more suitable substituents;

20 R^2 and R^3 are each independently H, halo or an alkoxy or lower alkyl group, where the alkoxy or lower alkyl group is unsubstituted or substituted with one or more suitable substituents;

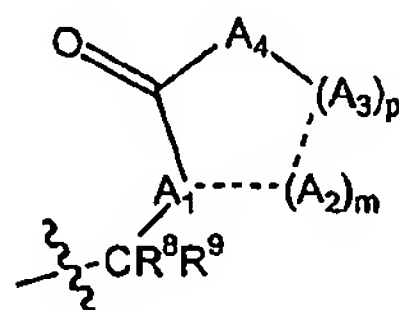
or R^1 together with R^2 form a cycloalkyl, heterocycloalkyl, aryl or heteroaryl ring, where the cycloalkyl, heterocycloalkyl, aryl or heteroaryl ring is unsubstituted or substituted with one or more suitable substituents;

25 R^4 and R^6 are each independently H or lower alkyl, unsubstituted or substituted with one or more suitable substituents;

- 24 -

R^5 is H or an alkyl group, unsubstituted or substituted with one or more suitable substituents;

R^7 is a moiety having the formula:



5 wherein:

R^8 and R^9 are each independently H or a lower alkyl group;

m is 0 or 1, provided that when m is 0 and R^1 together with R^2 form an aryl ring, the aryl ring is unsubstituted (e.g., R^1 together with R^2 and the pyrrole to which they are bound do not form a substituted indole);

10 p is an integer of from 0 to 5;

A_1 is CH or N;

when p is 1, 2, 3, 4, or 5, A_2 is $C(R^{10})(R^{11})$, $N(R^{12})$, S, S(O), S(O)₂, or O, and when p is 0, A_2 is $C(R^{10})(R^{11})(R^{12})$, $N(R^{10})(R^{12})$, S(R¹⁰), S(O)(R¹⁰), S(O)₂(R¹⁰), or O(R¹⁰) where each R^{10} , R^{11} and R^{12} is independently H or a lower alkyl group;

15 each A_3 present is independently $C(R^{10})(R^{11})$, $N(R^{12})$, S, S(O), S(O)₂, or O, where each R^{10} , R^{11} and R^{12} is independently H or a lower alkyl group;

when p is 1, 2, 3, 4, or 5, A_4 is $N(R^{13})$, $C(R^{10})(R^{11})$, or O, and when p is 0, A_4 is $N(R^{13})(R^{14})$, $C(R^{10})(R^{11})(R^{12})$, and O(R¹⁴), where each R^{10} , R^{11} and R^{12} is independently H or a lower alkyl group, each R^{13} is H or an alkyl, aryl, or acyl group, and each R^{14} is H or an alkyl or aryl group;

20 provided that no more than two heteroatoms occur consecutively in the above-depicted ring formed by A_1 , $(A_2)_m$, $(A_3)_p$, A_4 , and C=O, where each dotted line in the ring depicts a single bond when A_2 is present and a hydrogen atom when A_2 is absent; and

25 Z and Z¹ are each independently H, F, an alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group, where the alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group is unsubstituted or substituted with one or more suitable substituents, -C(O)R¹⁵, -CO₂R¹⁵, -CN, -C(O)NR¹⁵R¹⁶, -C(O)NR¹⁵OR¹⁶, -C(S)R¹⁵, -C(S)OR¹⁵, -C(S)NR¹⁵R¹⁶, -C(=NR¹⁵)R¹⁶, -C(=NR¹⁵)OR¹⁶, -NO₂, -SOR¹⁶, -SO₂R¹⁵, -SO₂NR¹⁵R¹⁶,

- 25 -

-SO₂(NR¹⁵)(OR¹⁶), -SONR¹⁵, -SO₃R¹⁵, -PO(OR¹⁵)₂, -PO(OR¹⁵)(OR¹⁶),
 -PO(NR¹⁵R¹⁶)(OR¹⁷), -PO(NR¹⁵R¹⁶)(NR¹⁷R¹⁸), -C(O)NR¹⁵NR¹⁶R¹⁷, -C(S)NR¹⁵NR¹⁶R¹⁷,
 where R¹⁵, R¹⁶, R¹⁷ and R¹⁸ are each independently H or an alkyl, cycloalkyl, aryl,
 heterocycloalkyl, acyl or thioacyl group, where the alkyl, cycloalkyl, aryl,

5 heterocycloalkyl, acyl or thioacyl group is unsubstituted or substituted with one or
 more suitable substituents, or where any two of the R¹⁵, R¹⁶, R¹⁷ and R¹⁸, taken together
 with the atoms to which they are bonded, form a heterocycloalkyl group, which is
 unsubstituted or substituted with one or more suitable substituents,

or Z and Z¹, together with the atoms to which they are bonded, form a
 10 cycloalkyl or heterocycloalkyl group, where Z and Z¹ are as defined above (except for
 moieties that cannot form the cycloalkyl or heterocycloalkyl group);

or a prodrug, pharmaceutically acceptable salt, pharmaceutically active
 metabolite, or pharmaceutically acceptable solvate of said compound.

In another embodiment of the compounds of the above formulas,

15 A₁ is CH or N;

A₂ is C(R¹⁰)(R¹¹), N(R¹²), S, S(O), S(O)₂, or O, where each R¹⁰, R¹¹ and R¹²
 is independently H or a lower alkyl group;

each A₃ present is independently C(R¹⁰)(R¹¹), N(R¹²), S, S(O), S(O)₂, or O,
 where each R¹⁰, R¹¹ and R¹² is independently H or a lower alkyl group;

20 when p is 1, 2, 3, 4, or 5, A₄ is N(R¹³), C(R¹⁰)(R¹¹), or O, and when p is 0,
 A₄ is N(R¹³)(R¹⁴), C(R¹⁰)(R¹¹)(R¹²), and O(R¹⁴), where each R¹⁰, R¹¹ and R¹² is
 independently H or a lower alkyl group, each R¹³ is H or an alkyl, aryl, or acyl group,
 and each R¹⁴ is H or an alkyl or aryl group;

provided that no more than two heteroatoms occur consecutively in the
 25 above-depicted ring formed by A₁, (A₂)_m, (A₃)_p, A₄, and C=O, where each dotted line
 in the ring depicts a single bond when A₂ is present and a hydrogen atom when A₂ is
 absent; and

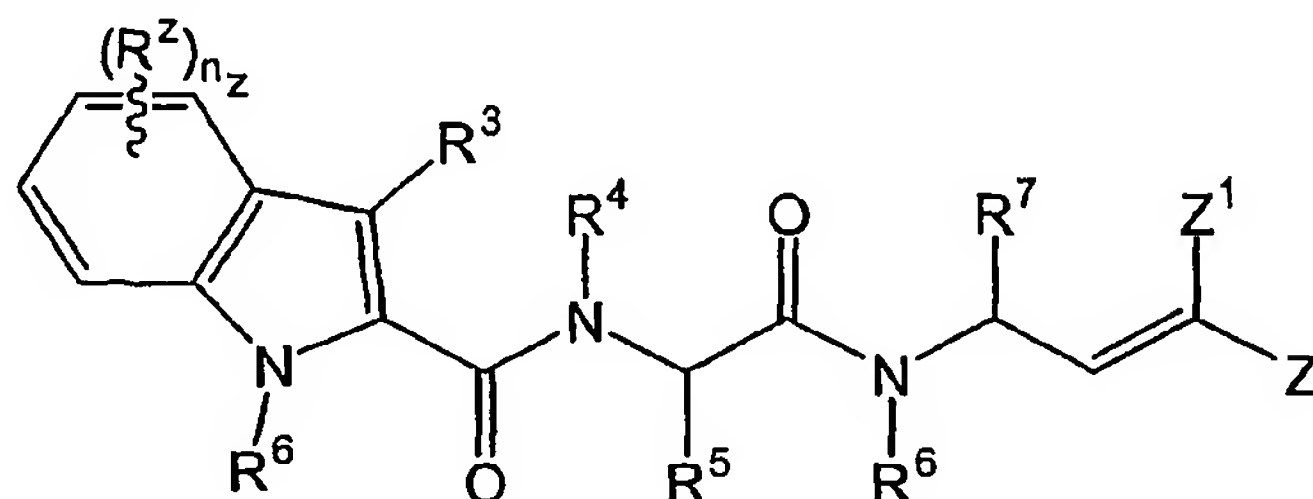
Z and Z¹ are each independently H, F, an alkyl, cycloalkyl,
 heterocycloalkyl, aryl or heteroaryl group, where the alkyl, aryl, cycloalkyl,
 30 heterocycloalkyl, aryl or heteroaryl group is unsubstituted or substituted with one or
 more suitable substituents, -C(O)R¹⁵, -CO₂R¹⁵, -CN, -C(O)NR¹⁵R¹⁶, -C(O)NR¹⁵OR¹⁶,

- 26 -

-C(S)R¹⁵, -C(S)NR¹⁵R¹⁶, -NO₂, -SOR¹⁶, -SO₂R¹⁵, -SO₂NR¹⁵R¹⁶, -SO₂(NR¹⁵)(OR¹⁶),
-SONR¹⁵, -SO₃R¹⁵, -PO(OR¹⁵)₂, -PO(OR¹⁵)(OR¹⁶), -PO(NR¹⁵R¹⁶)(OR¹⁷),
-PO(NR¹⁵R¹⁶)(NR¹⁷R¹⁸), -C(O)NR¹⁵NR¹⁶R¹⁷, -C(S)NR¹⁵NR¹⁶R¹⁷, where R¹⁵, R¹⁶, R¹⁷
and R¹⁸ are each independently H or an alkyl, cycloalkyl, aryl, heterocycloalkyl, acyl or
5 thioacyl group, where the alkyl, aryl, cycloalkyl, aryl, heterocycloalkyl, acyl or thioacyl
group is unsubstituted or substituted with one or more suitable substituents, or where
any two of the R¹⁵, R¹⁶, R¹⁷ and R¹⁸, taken together with the atoms to which they are
bonded, form a heterocycloalkyl group, which is unsubstituted or substituted with one
or more suitable substituents, or Z and Z¹, together with the atoms to which they are
10 bonded, form a cycloalkyl or heterocycloalkyl group, where Z and Z¹ are as defined
above. Preferably, in the compounds of Formulas IX and X, R¹ may be selected from
H and a lower alkyl, phenyl, naphthyl, pyridyl, quinoyl, isoquinoyl or isoxazoyl group,
where the lower alkyl, phenyl, naphthyl, pyridyl, quinoyl, isoquinoyl or isoxazoyl
group is unsubstituted or substituted with one or more substituents selected from alkyl
15 (but not as a substituent for alkyl), hydroxy, halo, haloalkyl, alkoxy, haloalkoxy and
alkylenedioxy moiety. Exemplary R¹ groups include, but are not limited to H, phenyl,
α-naphthyl, β-naphthyl, 2-chlorophenyl, 2-α,α,α-trifluoromethylphenyl, 3-chloro-6-
methoxyphenyl, 2,3-dichlorophenyl, 4-isoquinoyl, 3-iso-propylphenyl,
2,5-dimethoxyphenyl, 2-methoxyphenyl, 2-methylphenyl (o-tolyl), 2-bromophenyl,
20 3-pyridyl, 4-pyridyl, 3-methyl-isoxazol-5-yl, 3,3,3-trifluoroprop-1-yl, and
2,3-benzo[d]dioxolyl. Preferably, in the compounds of Formulas IX and X, R² and R³
may be each independently selected from H, halo, alkoxy, unsubstituted lower alkyl,
haloalkyl, and lower alkoxyalkyl. R⁴ and R⁶ may be each independently selected from
H, unsubstituted lower alkyl, haloalkyl and lower alkoxyalkyl.

- 27 -

Yet another preferred embodiment of this invention comprises the compounds depicted by the formula:

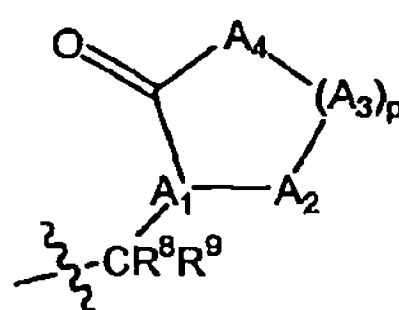


XI

wherein:

each R^2 is H or a suitable substituent and n_z is an integer from 1 to 4;

R^7 is a moiety having the formula:



wherein:

R^8 and R^9 are each independently H or a lower alkyl group;

p is an integer of from 1 to 5;

A_1 is CH or N;

when p is 1, 2, 3, 4, or 5, A_2 is $C(R^{10})(R^{11})$, $N(R^{12})$, S, $S(O)$, $S(O)_2$, or O, and

when p is 0, A_2 is $C(R^{10})(R^{11})(R^{12})$, $N(R^{10})(R^{12})$, $S(R^{10})$, $S(O)(R^{10})$, $S(O)_2(R^{10})$, or $O(R^{10})$ where each R^{10} , R^{11} and R^{12} is independently H or a lower alkyl group;

each A_3 present is independently $C(R^{10})(R^{11})$, $N(R^{12})$, S, $S(O)$, $S(O)_2$, or O, where each R^{10} , R^{11} and R^{12} is independently H or a lower alkyl group;

A_4 is $N(R^{13})$, $C(R^{10})(R^{11})$, or O, where R^{10} and R^{11} are each independently H or a lower alkyl group, and R^{13} is H or an alkyl, aryl or acyl group;

provided that no more than two heteroatoms occur consecutively in the above-depicted ring formed by A_1 , $(A_2)_m$, $(A_3)_p$, A_4 , and $C=O$; and

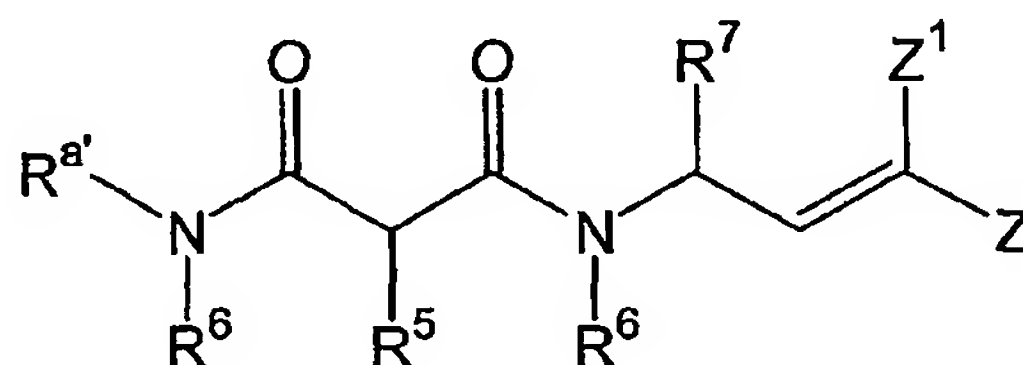
each R^3 , R^4 , R^5 , R^6 , Z and Z^1 are as defined above.

Preferably, in the compounds of Formula XI, each R^z is independently selected from H, halo, alkoxy, unsubstituted lower alkyl, haloalkyl, and lower alkoxyalkyl. R^3 may be independently selected from H, halo, alkoxy, unsubstituted

- 28 -

lower alkyl, haloalkyl and lower alkoxyalkyl and R^4 and R^6 may be each independently selected from H, unsubstituted lower alkyl, haloalkyl and lower alkoxyalkyl.

Another preferred embodiment of this invention comprise the compounds of Formula IV, wherein n is 1, depicted by the formula:



XII

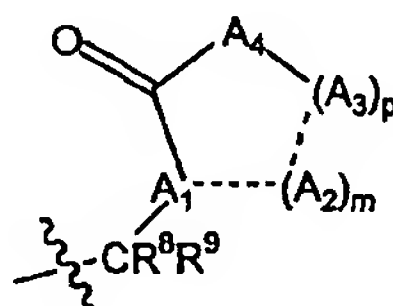
wherein:

R^a' is an alkyl, aryl, cycloalkyl, heterocycloalkyl or heteroaryl, where the alkyl, aryl, cycloalkyl, heterocycloalkyl, or heteroaryl group is unsubstituted or substituted with one or more suitable substituents;

R^5 is H or an alkyl group, unsubstituted or substituted with one or more suitable substituents,;

each R^6 is independently H or a lower alkyl group, unsubstituted or substituted with one or more suitable substituents,;

R^7 is a moiety having the formula:



wherein:

R^8 and R^9 are each independently H or a lower alkyl group;

m is 0 or 1;

p is an integer of from 0 to 5;

A_1 is CH or N;

when p is 1, 2, 3, 4, or 5, A_2 is $C(R^{10})(R^{11})$, $N(R^{12})$, S, $S(O)$, $S(O)_2$, or O, and when p is 0, A_2 is $C(R^{10})(R^{11})(R^{12})$, $N(R^{10})(R^{12})$, $S(R^{10})$, $S(O)(R^{10})$, $S(O)_2(R^{10})$, or $O(R^{10})$ where each R^{10} , R^{11} and R^{12} is independently H or a lower alkyl group;

- 29 -

each A_3 present is independently $C(R^{10})(R^{11})$, $N(R^{12})$, S , $S(O)$, $S(O)_2$, or O , where each R^{10} , R^{11} and R^{12} is independently H or a lower alkyl group;

when p is 1, 2, 3, 4, or 5, A_4 is $N(R^{13})$, $C(R^{10})(R^{11})$, or O , and when p is 0, A_4 is $N(R^{13})(R^{14})$, $C(R^{10})(R^{11})(R^{12})$, and $O(R^{14})$, where each R^{10} , R^{11} and R^{12} is
 5 independently H or a lower alkyl group, each R^{13} is H or an alkyl, aryl, or acyl group, and each R^{14} is H or an alkyl or aryl group;

provided that no more than two heteroatoms occur consecutively in the above-depicted ring formed by A_1 , $(A_2)_m$, $(A_3)_p$, A_4 , and $C=O$, where each dotted line in the ring depicts a single bond when A_2 is present and a hydrogen atom when A_2 is
 10 absent; and

Z and Z^1 are each independently H , F , an alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group, where the alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group is unsubstituted or substituted with one or more suitable substituents,
 15 $-C(O)R^{15}$, $-CO_2R^{15}$, $-CN$, $-C(O)NR^{15}R^{16}$, $-C(O)NR^{15}OR^{16}$, $-C(S)R^{15}$, $-C(S)OR^{15}$,
 $-C(S)NR^{15}R^{16}$, $-C(=NR^{15})R^{16}$, $-C(=NR^{15})OR^{16}$, $-NO_2$, $-SOR^{16}$, $-SO_2R^{15}$, $-SO_2NR^{15}R^{16}$,
 $-SO_2(NR^{15})(OR^{16})$, $-SONR^{15}$, $-SO_3R^{15}$, $-PO(OR^{15})_2$, $-PO(OR^{15})(OR^{16})$,
 $-PO(NR^{15}R^{16})(OR^{17})$, $-PO(NR^{15}R^{16})(NR^{17}R^{18})$, $-C(O)NR^{15}NR^{16}R^{17}$, $-C(S)NR^{15}NR^{16}R^{17}$,
 where R^{15} , R^{16} , R^{17} and R^{18} are each independently H or an alkyl, cycloalkyl, aryl,
 heterocycloalkyl, acyl or thioacyl group, where the alkyl, cycloalkyl, aryl,
 20 heterocycloalkyl, acyl or thioacyl group is unsubstituted or substituted with one or more suitable substituents, or where any two of the R^{15} , R^{16} , R^{17} and R^{18} , taken together with the atoms to which they are bonded, form a heterocycloalkyl group, which is unsubstituted or substituted with one or more suitable substituents,

or Z and Z^1 , together with the atoms to which they are bonded, form a
 25 cycloalkyl or heterocycloalkyl group, where Z and Z^1 are as defined above (except for moieties that cannot form the cycloalkyl or heterocycloalkyl group);

or a prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate of said compound.

In another embodiment of the compounds of the above formulas, Z and Z^1
 30 are each independently H , F , an alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group, where the alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group is

- 30 -

unsubstituted or substituted with one or more suitable substituents, $-C(O)R^{15}$, $-CO_2R^{15}$,
 $-CN$, $-C(O)NR^{15}R^{16}$, $-C(O)NR^{15}OR^{16}$, $-C(S)R^{15}$, $-C(S)NR^{15}R^{16}$, $-NO_2$, $-SOR^{16}$,
 $-SO_2R^{15}$, $-SO_2NR^{15}R^{16}$, $-SO_2(NR^{15})(OR^{16})$, $-SONR^{15}$, $-SO_3R^{15}$, $-PO(OR^{15})_2$,
 $-PO(OR^{15})(OR^{16})$, $-PO(NR^{15}R^{16})(OR^{17})$, $-PO(NR^{15}R^{16})(NR^{17}R^{18})$, $-C(O)NR^{15}NR^{16}R^{17}$,
 5 $-C(S)NR^{15}NR^{16}R^{17}$, where R^{15} , R^{16} , R^{17} and R^{18} are independently H or an alkyl,
 cycloalkyl, aryl, heterocycloalkyl, acyl or thioacyl group, where the alkyl, cycloalkyl,
 aryl, heterocycloalkyl, acyl or thioacyl group is unsubstituted or substituted with one or
 more suitable substituents, or where any two of the R^{15} , R^{16} , R^{17} and R^{18} , taken together
 with the atoms to which they are bonded, form a heterocycloalkyl group, which is
 10 unsubstituted or substituted with one or more suitable substituents, or Z and Z^1 ,
 together with the atoms to which they are bonded, form a cycloalkyl or
 heterocycloalkyl group, where Z and Z^1 are as defined above.

Preferably, in the compounds of Formula XII, $R^{a'}$ may be selected from H,
 lower alkyl, phenyl, naphthyl, pyridyl, quinoyl, isoquinoyl and isoxazoyl, each of
 15 which may be substituted by alkyl (but not as a substituent for alkyl), hydroxy, halo,
 haloalkyl, alkoxy, haloalkoxy and alkylenedioxy. Each R^6 may be independently
 selected from H, unsubstituted lower alkyl, haloalkyl and loweralkoxyalkyl.

If an inventive compound is a base, a desired salt may be prepared by any
 suitable method known in the art, including treatment of the free base with an
 20 inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid,
 phosphoric acid, and the like, or with an organic acid, such as acetic acid, maleic acid,
 succinic acid, mandelic acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid,
 glycolic acid, salicylic acid, pyranosidyl acid, such as glucuronic acid or galacturonic
 acid, alpha-hydroxy acid, such as citric acid or tartaric acid, amino acid, such as
 25 aspartic acid or glutamic acid, aromatic acid, such as benzoic acid or cinnamic acid,
 sulfonic acid, such as p-toluenesulfonic acid or ethanesulfonic acid, or the like.

If an inventive compound is an acid, a desired salt may be prepared by any
 suitable method known to the art, including treatment of the free acid with an
 inorganic or organic base, such as an amine (primary, secondary, or tertiary); an alkali
 30 metal or alkaline earth metal hydroxide; or the like. Illustrative examples of suitable
 salts include organic salts derived from amino acids such as glycine and arginine;

ammonia; primary, secondary, and tertiary amines; and cyclic amines, such as piperidine, morpholine, and piperazine; as well as inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum, and lithium.

5 All compounds of this invention contain at least one chiral center and may exist as single stereoisomers (e.g., single enantiomers or diastereomers), any mixture of stereoisomers (e.g., any mixture of enantiomers or diastereomers) or racemic mixtures thereof. All such single stereoisomers, mixtures and racemates are intended to be encompassed within the broad scope of the present invention. Where the
10 stereochemistry of the chiral carbons present in the chemical structures illustrated herein is not specified, the chemical structure is intended to encompass compounds containing either stereoisomer of each chiral carbon. When used to describe a particular compound, the term "optically pure" is used herein to indicate that the compound is substantially enantiomerically or diastereomerically pure. Compounds that are
15 substantially enantiomerically pure contain at least 90% of a single isomer and preferably contain at least 95% of a single isomer. Compounds that are substantially diastereomerically pure contain at least 90% of a single isomer of each chiral carbon center present in the diastereomer, and preferably contain at least 95% of a single isomer of each chiral carbon. More preferably, when an optically active compound is
20 desired, it contains at least 97.5% of a single isomer and, most preferably, at least 99% of the single isomer. Compounds identified herein as single stereoisomers are meant to describe compounds that are present in a form that contains at least 90% of a single isomer. The term "racemic" or "racemic mixture" refers to a mixture of equal amounts of enantiomeric compounds, which encompasses mixtures of enantiomers
25 and mixtures of enantiomeric diastereomers. The compounds of this invention may be obtained in stereochemically (e.g., enantiomerically or diastereomerically) pure or substantially stereochemically pure form. Such compounds may be obtained synthetically, according to the procedures described herein using optically pure or substantially optically pure materials. Alternatively, these compounds may be
30 obtained by resolution/separation of a mixture of stereoisomers, including racemic mixtures, using conventional procedures. Exemplary methods that may be useful for

the resolution/separation of stereoisomeric mixtures include chromatography and crystallization/re-crystallization. Other useful methods may be found in "Enantiomers, Racemates, and Resolutions," J. Jacques et al., 1981, John Wiley and Sons, New York, NY. Preferred stereoisomers of the compounds of this invention are described herein.

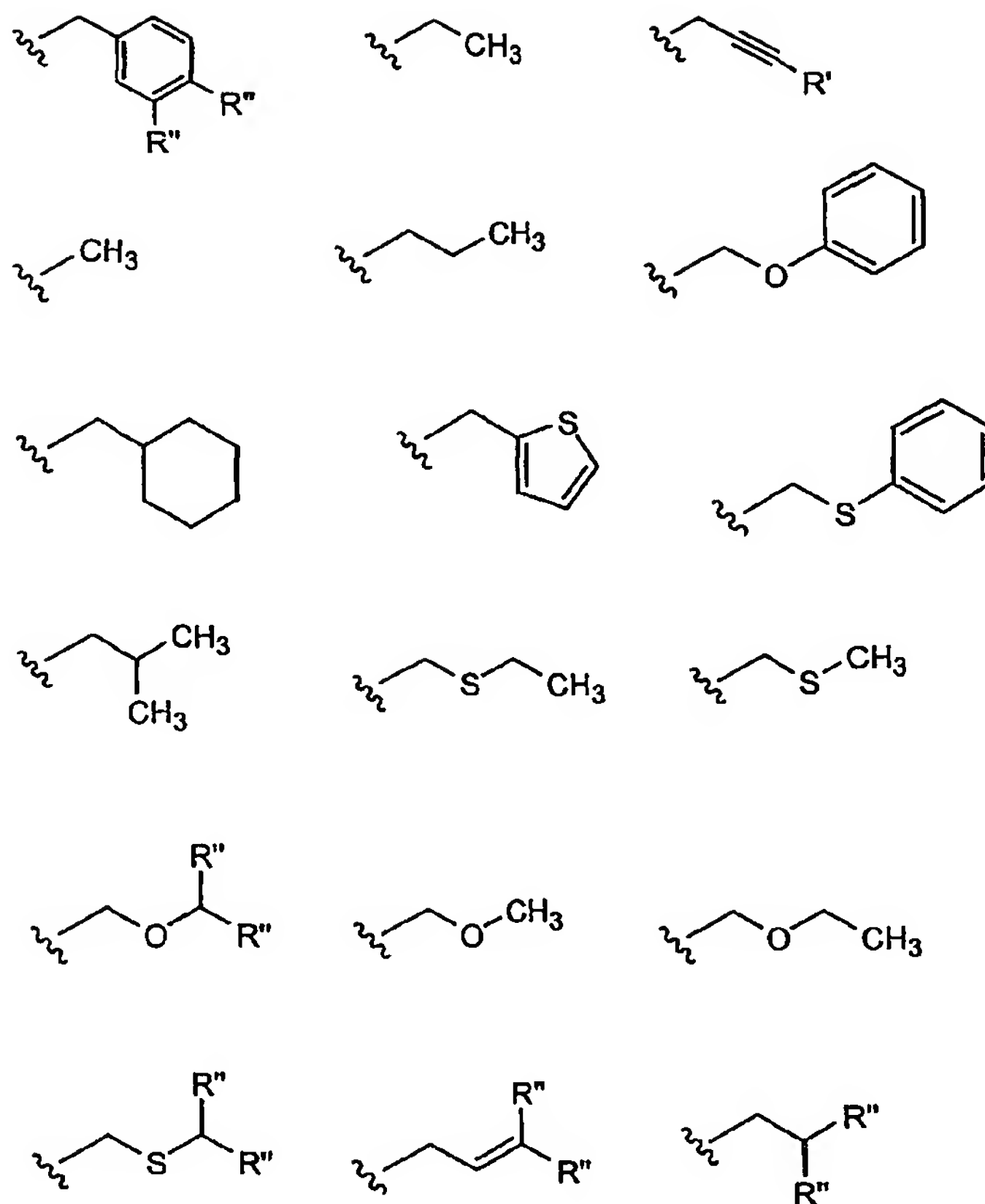
5 In especially preferred embodiments of Formulas V, VI, VII, VIII, IX, X, XI and XII, R^5 (or R^x or R^y in Formulas II, III and VI) is H or an unsubstituted alkyl group or an optionally substituted lower alkyl group, where these groups are comprised of a straight- or branched-chain saturated hydrocarbon group, a straight- or branched-chain substituted saturated hydrocarbon group, or group comprised of a straight- or
10 branched-chain saturated hydrocarbon moiety and an unsaturated hydrocarbon moiety. When R^5 or R^x/R^y is a substituted alkyl group, the point of attachment of R^5 or R^x/R^y is via a saturated hydrocarbon moiety. When R^5 or R^x/R^y is a substituted saturated hydrocarbon group, the saturated hydrocarbon group may be optionally substituted with a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, an
15 alkoxy group, an aryloxy group, an alkylthio group, an arylthio group, where each alkyl, cycloalkyl, aryl, heterocycloalkyl or heteroaryl moiety thereof may be optionally substituted. When R^5 or R^x/R^y is comprised of a saturated hydrocarbon moiety and an unsaturated hydrocarbon moiety, the saturated hydrocarbon moiety may be bound to an unsaturated hydrocarbon moiety containing one or more double-bonds or triple-bonds,
20 the terminal positions of which may be substituted by the substituents described above, or may contain additional straight- or branched-chain saturated hydrocarbon moieties. Preferably, the unsaturated hydrocarbon moiety contains one double-bond or one triple-bond, the terminal position(s) of which may optionally contain a straight- or branched-chain saturated hydrocarbon moiety. Preferably, if the unsaturated
25 hydrocarbon moiety contains a double-bond, both terminal positions of the double bond contain a straight- or branched-chain saturated hydrocarbon moiety. In especially preferred embodiments, R^5 or R^x/R^y is H or a lower alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl group, or a group comprised of a straight-chain saturated hydrocarbon moiety and an unsaturated hydrocarbon moiety, where the alkyl, arylalkyl,
30 heteroarylalkyl, cycloalkylalkyl group is unsubstituted or substituted with one or more suitable substituents. Preferably, R^5 or R^x/R^y is H or substituted or unsubstituted

- 33 -

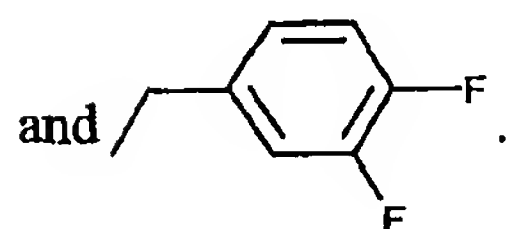
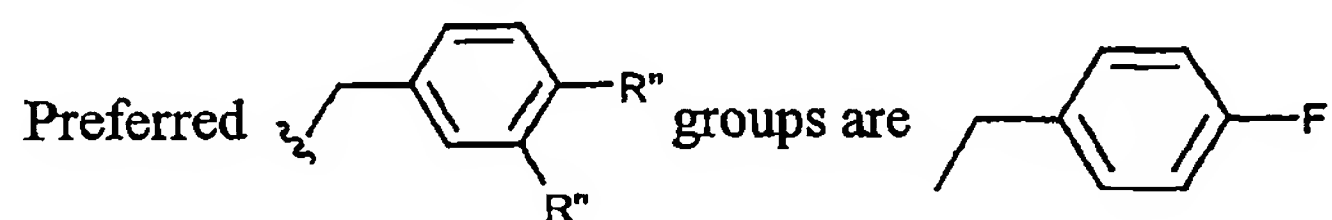
5 methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, -methylcyclohexyl, substituted or unsubstituted -methylthienyl or substituted or unsubstituted benzyl, where the methyl, ethyl, propyl, propenyl, butenyl or cyclohexyl moiety thereof is optionally substituted with one or more substituents independently selected from lower alkoxy, hydroxy, amino, alkylamino or dialkylamino and halogen, the phenyl moiety of the substituted benzyl is substituted by one or more substituents independently selected from lower alkyl, lower alkoxy, hydroxy, amino, alkylamino or dialkylamino and halogen and the thienyl moiety of the substituted -methylthienyl is substituted by one or more substituents independently selected from lower alkyl, lower alkoxy, hydroxy, amino, alkylamino, dialkylamino and halogen. When R⁵ or R^x/R^y is substituted methyl, the methyl (methylene) moiety may be substituted with an alkoxy group, an aryloxy group, an alkylthio group or an arylthio group. Most preferably, R⁵ or R^x/R^y is H, ethyl, 2-propyn-1-yl, -methylcyclohexyl, or substituted or unsubstituted benzyl, where the phenyl moiety of the substituted benzyl is substituted by one or more substituents independently selected from lower alkyl, lower alkoxy and halogen.

In the especially preferred embodiments of Formulas V, VI, VII, VIII, XI, XII and XII, R⁵ (or R^x or R^y in Formulas II, III and VI) is selected from H and:

- 34 -



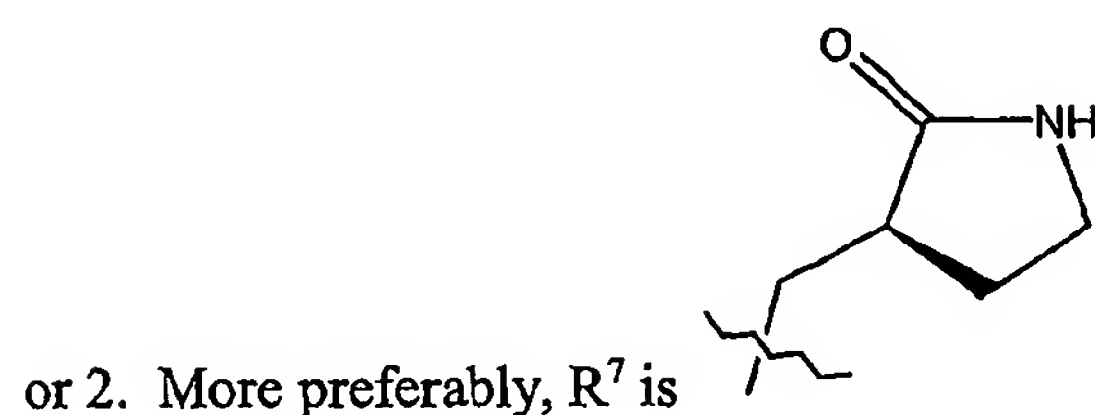
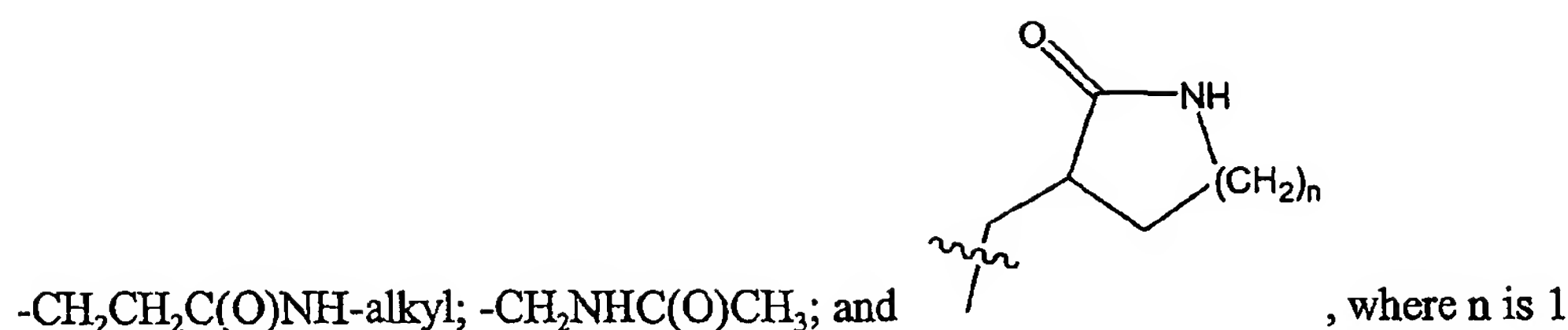
wherein R' may be H or alkyl and each R'' may be H or independently selected from lower alkyl, lower alkoxy, hydroxy, amino, alkylamino or dialkylamino, and halogen.



5

In especially preferred embodiments of Formulas V, VI, VII, VIII, IX, X, XI and XII, R⁷ (or R⁶ in Formulas I, II, III and VI) is selected from -CH₂CH₂C(O)NH₂;

- 35 -



5 Preferably, in each of the formulas described herein, Z and Z¹ are each independently H, alkyl, where the alkyl is unsubstituted or substituted with one or more suitable substituents, -CO₂R¹⁵ (in Formulas V to XII) or -CO₂R¹ (in Formulas I to VI), where R¹ and R¹⁵ are as defined above, or Z and Z¹, taken together with the atom to which they are attached, form a heterocycloalkyl group, as defined above, which

10 may be optionally substituted. In one useful embodiment of the compounds of this invention, Z and/or Z¹ may be -C(S)ORⁿ or -C(S)OR¹⁹, where Rⁿ and R¹⁹ are as defined above. Such compounds may be prepared using procedures described in K. Hartke, et al., *Leibigs Ann. Chem.*, 321-330 (1989) and K. Hartke, et al., *Synthesis*, 960-961 (1985). More preferably, the heterocycloalkyl group may optionally contain O, N, S

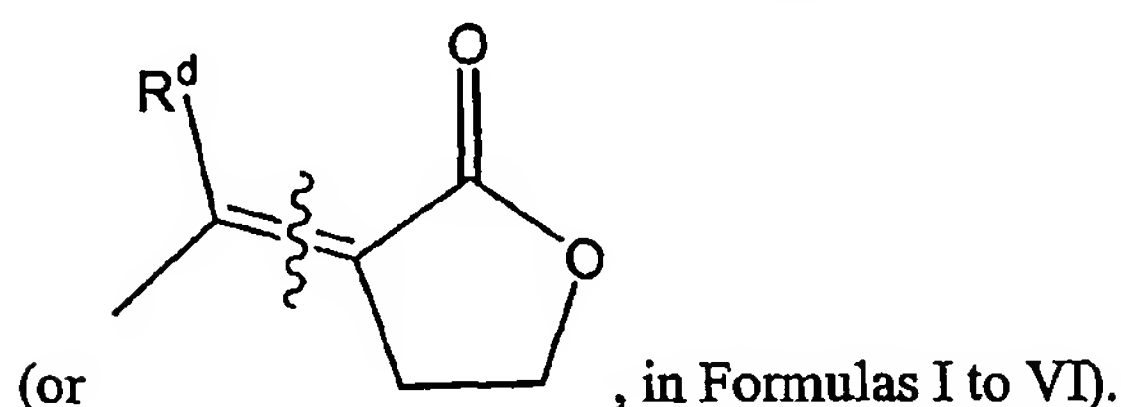
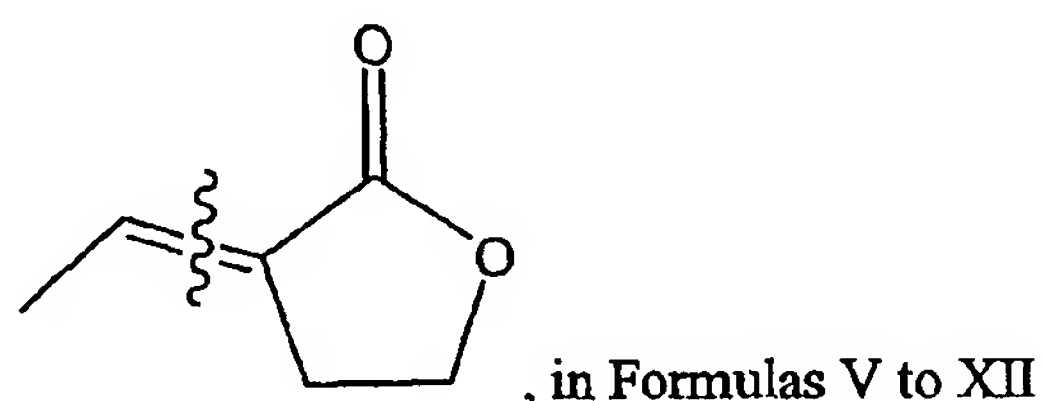
15 and/or P and may be substituted by one or more of oxo (keto) or thioketo. In another preferred embodiment of this invention, Z and Z¹ are each independently selected from H, lower alkyl which is unsubstituted or substituted with one or more suitable substituents, -CO₂H, -CO₂-alkyl and -CO₂-cycloalkyl, or taken together with the atom to which they are attached form a heterocycloalkyl group, which is optionally

20 substituted with one or more of keto or thioketo. In other preferred embodiments of this invention, Z and Z¹ are not both H. Most preferably, Z¹ is H or lower alkyl and Z is a -CO₂H, -CO₂-alkyl, -CO₂-alkylaryl, -CO₂-alkylheteroaryl, -CO₂-cycloalkyl group, where the lower alkyl, -alkyl, -cycloalkyl, -alkylaryl and -alkylheteroaryl moieties thereof are unsubstituted or substituted with one or more suitable substituents, or Z¹

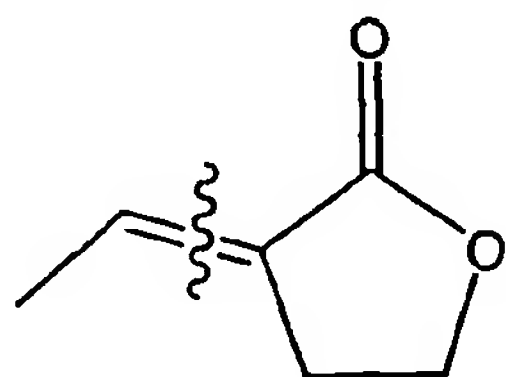
25 and Z taken together with the atom to which they are attached form a heterocycloalkyl group, which may be optionally substituted. Exemplary Z groups include, but are not

- 36 -

limited to: substituted and unsubstituted $\text{-CO}_2\text{-alkyl}$ groups, which include straight- and branched-chain alkyl groups such as ethoxycarbonyl, t-butoxycarbonyl, isopropoxycarbonyl and (2,2-dimethylpropyl)-oxycarbonyl, where the ethoxy, t-butoxy, isopropoxy, and (2,2-dimethylpropyl)-oxy moieties thereof are unsubstituted or substituted with one or more suitable substituents; and include substituted and unsubstituted straight and branched-chain arylalkyl and heteroarylalkyl groups, such as benzyloxycarbonyl and pyridylmethylenoxycarbonyl, where the benzyl and pyridylmethylene moieties thereof are unsubstituted or substituted with one or more suitable substituents; and include substituted and unsubstituted $\text{-CO}_2\text{-cycloalkyl}$ groups such as cyclobutyloxycarbonyl, cyclopentyloxycarbonyl, cyclohexyloxycarbonyl and cycloheptyloxycarbonyl groups, where the cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl moieties thereof are unsubstituted or substituted with one or more suitable substituents, or Z^1 and Z taken together with the atom to which they are attached form



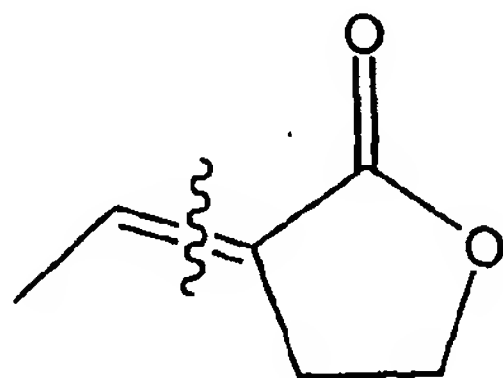
In another embodiment of this invention, Z^1 is H and Z is $\text{-CO}_2\text{CH}_2\text{CH}_3$, $\text{-CO}_2(\text{CH}(\text{CH}_3)_2)$, $\text{-CO}_2(\text{C}(\text{CH}_3)_3)$, $\text{-CO}_2\text{CH}_2(\text{C}(\text{CH}_3)_3)$, $\text{-CO}_2(\text{cyclo-C}_5\text{H}_9)$ or Z^1 and Z taken together with the atom to which they are attached form



In yet another embodiment of this invention, Z^1 is H and Z is selected from ethoxycarbonyl, t-butoxycarbonyl, isopropoxycarbonyl, (2,2-dimethylpropyl)-

- 37 -

oxycarbonyl, benzyloxycarbonyl, pyridylmethylenoxycarbonyl, cyclobutyloxycarbonyl, cyclopentyloxycarbonyl, cyclohexyloxycarbonyl and cycloheptyloxycarbonyl, or Z^1 and Z taken together with the atom to which they are attached form



5

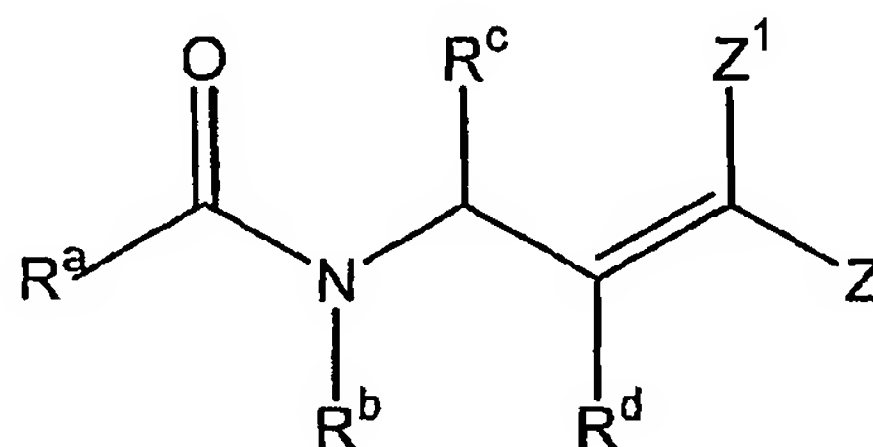
In the compounds of each of the above-described Formulas, R^e and R^7 are defined to provide structures where m is 1 and p is 1-5 (i.e., both A_2 and A_3 are present), m is 0 and p is 0 (i.e., both A_2 and A_3 are absent), m is 0 and p is 1-5 (i.e., A_2 is absent and A_3 is present) and m is 1 and p is 0 (i.e., A_2 is present and A_3 is absent). Accordingly, one of ordinary skill in the art will recognize that when both A_2 and A_3 are present (m is 1 and p is 1-5), the dotted line between A_1 and A_2 represents a bond and the dotted line between A_2 and A_3 represents a bond and when both A_2 and A_3 are absent (m is 0 and p is 0); A_2 , A_3 and the dotted line between these substituents are not present), the remaining dotted line in the structure between A_1 and A_2 represents a hydrogen (e.g., A_1 is CH_2 or NH). In embodiments of this invention when A_2 is absent and A_3 is present (m is 0 and p is 1-5), the dotted line between A_1 and A_2 represents a hydrogen and the dotted line between A_2 and A_3 represents a hydrogen (e.g., A_1 is CH_2 or NH and A_3 is $CH(R^5)(R^h)$, $NH(R^i)$, SH, $S(O)H$, $S(O)_2H$, or OH or $CH(R^{10})(R^{11})$, $NH(R^{12})$, SH, $S(O)H$, $S(O)_2H$, or OH); and when A_2 is present and A_3 is absent (m is 1 and p is 0), the dotted line between A_1 and A_2 represents a bond and A_2 is $C(R^5)(R^h)(R^i)$, $N(R^5)(R^i)$, $S(R^5)$, $S(O)(R^5)$, $S(O)_2(R^5)$, or $O(R^5)$ or A_2 is $C(R^{10})(R^{11})(R^{12})$, $N(R^{10})(R^{12})$, $S(R^{10})$, $S(O)(R^{10})$, $S(O)_2(R^{10})$, or $O(R^{10})$ or the dotted line between A_2 and A_3 represents a hydrogen and A_2 is $CH(R^5)(R^h)$, $NH(R^i)$, SH, $S(O)H$, $S(O)_2H$, or OH or A_2 is $CH(R^{10})(R^{11})$, $NH(R^{12})$, SH, $S(O)H$, $S(O)_2H$, or OH. In preferred embodiments of the compounds of each of the above-described Formulas, m is 1 and p is 1 or 2 or m is 0 and p is 0 or m is 1 and p is 0. More preferably, when m

25

is 1 and p is 1 or 2, A_2 and A_3 are both $C(R^5)(R^h)$ or $C(R^{10})(R^{11})$, respectively. More preferably, m is 1 and p is 1.

In the compounds of Formulas I to IV, R^d and each R^b are preferably H, in the compounds of Formulas V to XI, each R^4 and R^6 are preferably H and in the compounds of Formula XIII, each R^6 is preferably H.

Other embodiments of this invention comprise compounds having the formula:



I

10 wherein:

R^a is (C₁-C₄)alkylcarbonyl-(C₁-C₄)alkyl,
(C₃-C₈)cycloalkylcarbonyl-(C₁-C₄)alkyl, arylcarbonyl-(C₁-C₄)alkyl,
heteroarylcarbonyl-(C₁-C₄)alkyl, (C₁-C₄)alkylcarbonylamino-(C₁-C₄)alkyl, (C₃-C₈)
cycloalkylcarbonylamino-(C₁-C₄)alkyl, heterocycloalkylcarbonylamino-(C₁-C₄)alkyl,
15 arylcarbonylamino-(C₁-C₄)alkyl, heteroarylcarbonylamino-(C₁-C₄)alkyl, (C₁-C₄
alkylaminocarbonyl-(C₁-C₄)alkyl, (C₃-C₈)cycloalkylaminocarbonyl-(C₁-C₄)alkyl,
heterocycloalkylaminocarbonyl-(C₁-C₄)alkyl, arylaminocarbonyl-(C₁-C₄)alkyl,
heteroarylaminocarbonyl-(C₁-C₄)alkyl, wherein each (C₁-C₄)alkyl, (C₃-C₈)cycloalkyl,
heterocycloalkyl, aryl and heteroaryl moiety thereof is unsubstituted or substituted
20 with one or more suitable substituents; preferably R^a is
(C₁-C₄)alkylcarbonyl-(C₁-C₄)alkyl, (C₅-C₆)cycloalkylcarbonyl-(C₁-C₄)alkyl,
arylcarbonyl-(C₁-C₄)alkyl, heteroarylcarbonyl-(C₁-C₄)alkyl,
(C₁-C₄)alkylcarbonylamino-(C₁-C₄)alkyl, C₃-C₈ cycloalkylcarbonylamino-(C₁-C₄)alkyl,
heterocycloalkylcarbonylamino-(C₁-C₄)alkyl, arylcarbonylamino-(C₁-C₄)alkyl,
25 heteroarylcarbonylamino-(C₁-C₄)alkyl, (C₁-C₄)alkylaminocarbonyl-(C₁-C₄)alkyl,
(C₅-C₆)cycloalkylaminocarbonyl-(C₁-C₄)alkyl, heterocycloalkylaminocarbonyl-
(C₁-C₄)alkyl, arylaminocarbonyl-(C₁-C₄)alkyl, heteroarylaminocarbonyl-(C₁-C₄)alkyl,
wherein each (C₁-C₄)alkyl, (C₃-C₈)cycloalkyl, heterocycloalkyl, aryl and heteroaryl

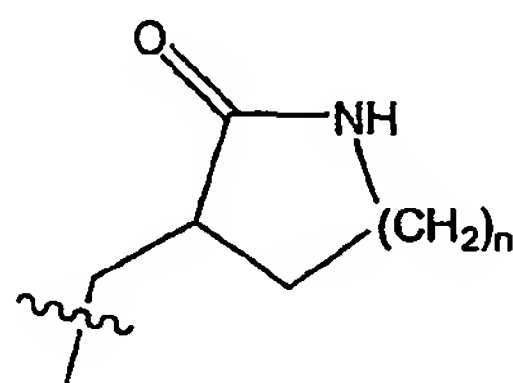
- 39 -

moiety thereof is unsubstituted or substituted with one or more suitable substituents;
 more preferably, R^a is (C₁-C₄)alkylcarbonyl-(C₁-C₄)alkyl, phenylcarbonyl-(C₁-C₄)alkyl,
 naphthylcarbonyl-(C₁-C₄)alkyl, pyrrolylcarbonyl-(C₁-C₄)alkyl,
 indolylcarbonyl-(C₁-C₄)alkyl, (C₁-C₄)alkylcarbonylamino-(C₁-C₄)alkyl,
 5 pyrrolylcarbonylamino-(C₁-C₄)alkyl, indolylcarbonylamino-(C₁-C₄)alkyl,
 phenylcarbonylamino-(C₁-C₄)alkyl, naphthylcarbonylamino-(C₁-C₄)alkyl,
 (C₁-C₄)alkylaminocarbonyl-(C₁-C₄)alkyl, pyrrolylaminocarbonyl-(C₁-C₄)alkyl,
 phenylaminocarbonyl-(C₁-C₄)alkyl, naphthylaminocarbonyl-(C₁-C₄)alkyl, wherein
 each (C₁-C₄)alkyl, phenyl, naphthyl, pyrrolyl, and indolyl moiety thereof is
 10 unsubstituted or substituted with one or more substituents independently selected from
 halo, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, methylenedioxy,
 aryl, heterocycloalkyl, and heteroaryl, where the aryl, heterocycloalkyl or heteroaryl is
 unsubstituted or substituted by one or more substituents independently selected from
 halo, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy and
 15 methylenedioxy; and preferably, where said indolyl moiety thereof is substituted with
 one or two substituents independently selected from halo, C₁-C₄ alkoxy, unsubstituted
 C₁-C₄ alkyl and C₁-C₄ haloalkyl;

R^b and R^d are each independently H or C₁-C₄ alkyl; preferably R^b and R^d are
 each H;

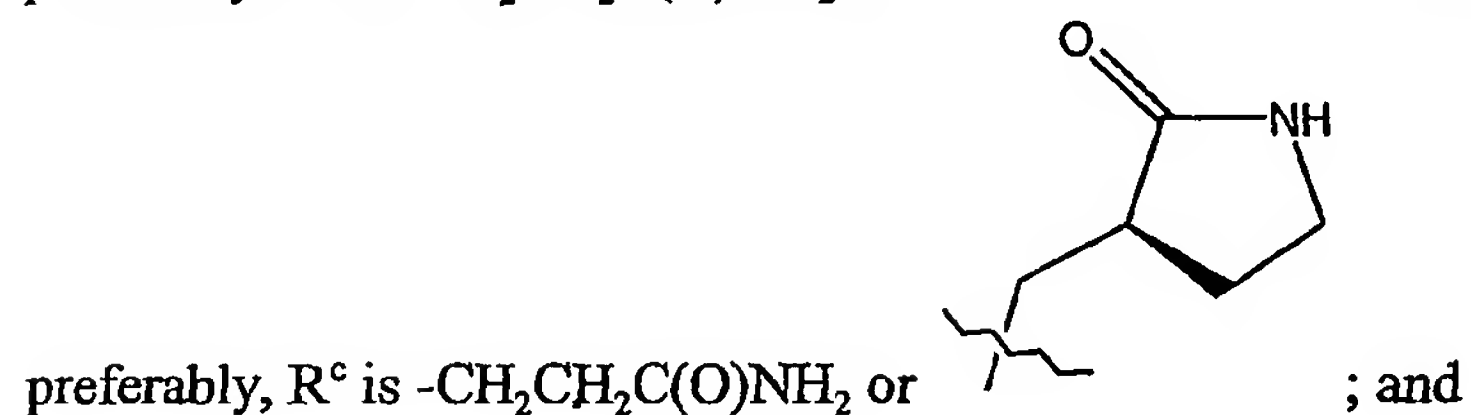
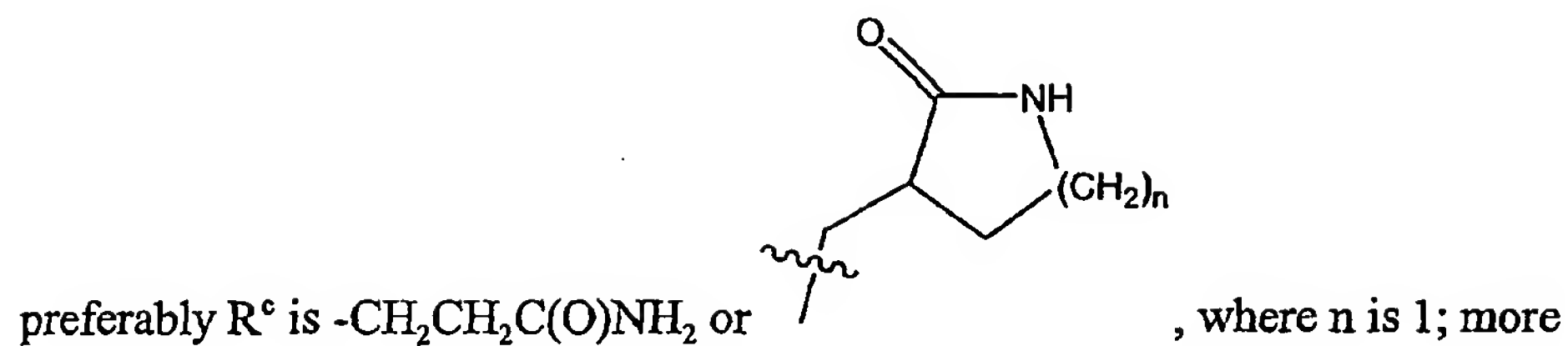
20 R^c is selected from -CH₂CH₂C(O)NH₂; -CH₂CH₂C(O)NH-alkyl;

-CH₂NHC(O)CH₃; and

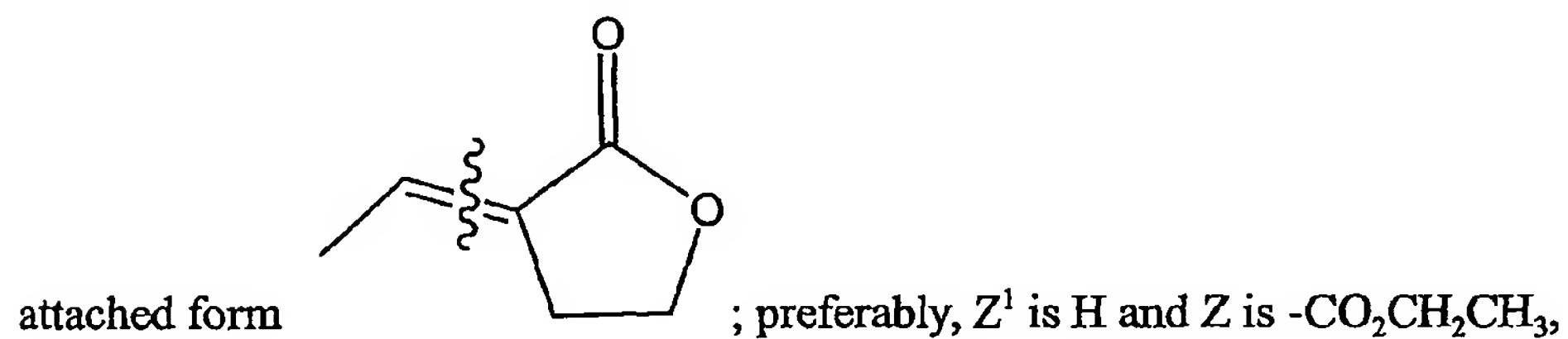


, where n is 1 or 2;

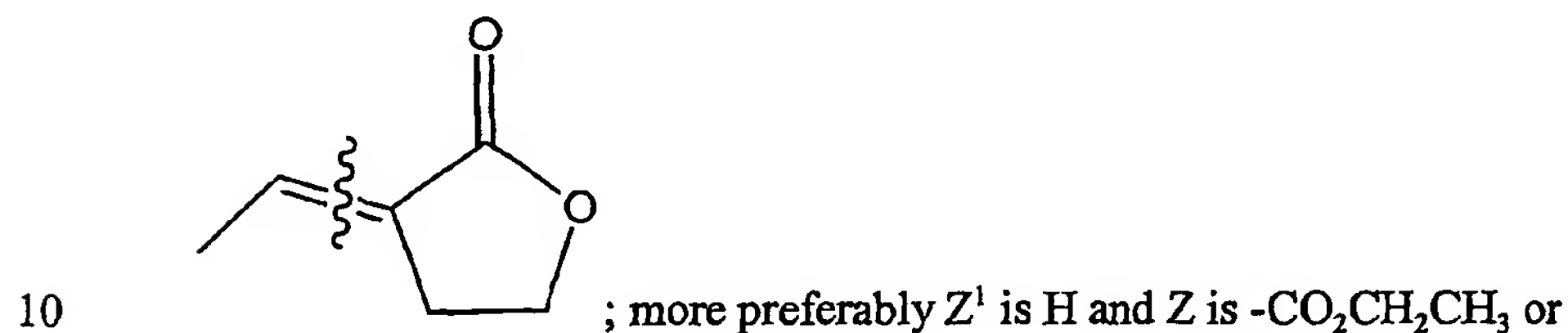
- 40 -



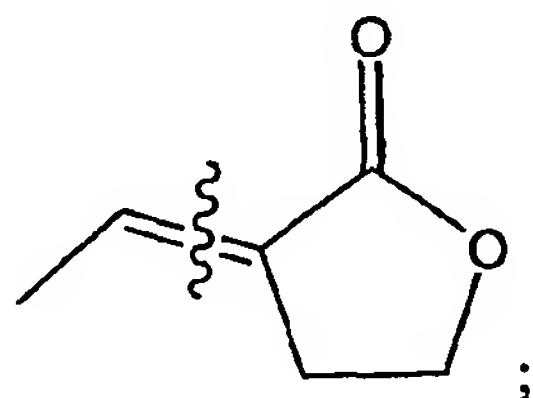
Z^1 is H or C_1 - C_4 alkyl and Z is $-\text{CO}_2$ -alkyl, $-\text{CO}_2$ -cycloalkyl, $-\text{CO}_2$ -alkylaryl or
5 $-\text{CO}_2$ -alkylheterocycloaryl, or Z^1 and Z taken together with the atom to which they are



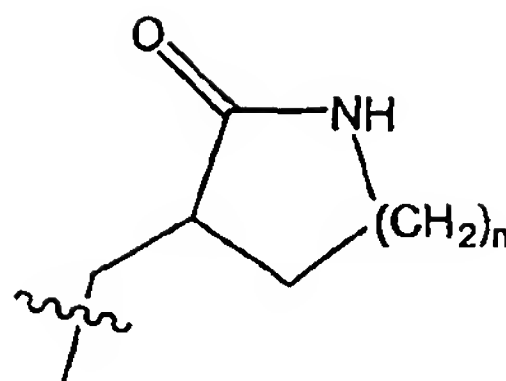
$-\text{CO}_2(\text{CH}(\text{CH}_3)_2)$, $-\text{CO}_2(\text{C}(\text{CH}_3)_3)$, $-\text{CO}_2\text{CH}_2(\text{C}(\text{CH}_3)_3)$, $-\text{CO}_2(\text{cyclo-C}_5\text{H}_9)$ or Z^1 and Z
taken together with the atom to which they are attached form



Z^1 and Z taken together with the atom to which they are attached form

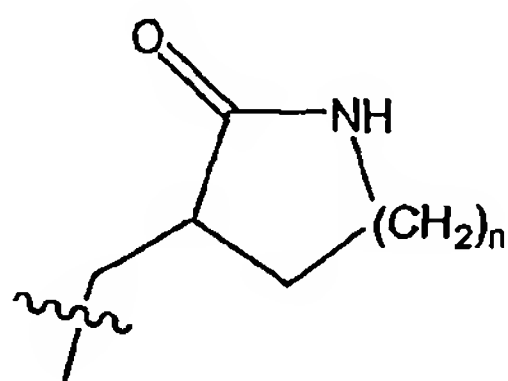


- 41 -

provided that R^c is

, where n is 1 or 2, when

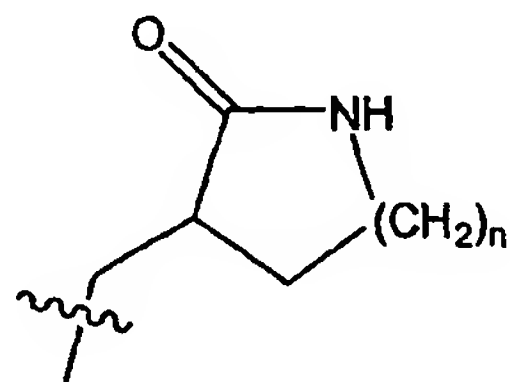
R^a is an indolylcarbonylamino-(C₁-C₄)alkyl group where the indolyl moiety thereof is substituted with one or more suitable substituents or R^a is is not an amino-substituted (C₁-C₄)alkylcarbonylamino-(C₁-C₄)alkyl or R^a is is not an amino-substituted (C₁-C₄)alkylcarbonyl-(C₁-C₄)alkyl; and R^c is selected from -CH₂CH₂C(O)NH₂; -CH₂CH₂C(O)NH-alkyl; -CH₂NHC(O)CH₃; and



, where n is 1 or 2, when

- 10 R^a is an indolylcarbonylamino-(C₁-C₄)alkyl group where the indolyl moiety thereof is unsubstituted or R^a is a (C₁-C₄) alkylaminocarbonyl-(C₁-C₄)alkyl, (C₃-C₈)cycloalkylaminocarbonyl-(C₁-C₄)alkyl, heterocycloalkylaminocarbonyl-(C₁-C₄)alkyl, arylaminocarbonyl-(C₁-C₄)alkyl, heteroarylaminocarbonyl-(C₁-C₄)alkyl, or heteroarylcarbonylamino-(C₁-C₄)alkyl group, wherein each (C₁-C₄)alkyl, (C₃-C₈)cycloalkyl, heterocycloalkyl, aryl and heteroaryl moiety thereof is unsubstituted or substituted with one or more suitable substituents;
- 15 or a prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate of said compound.

Preferably, in the compounds of Formula I, as defined above,



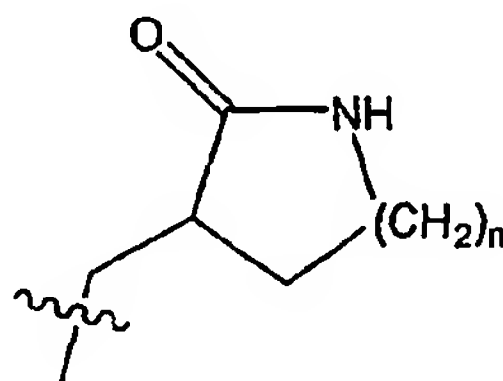
- 20 R^c is

, where n is 1, when

R^a is an indolylcarbonylamino-(C₁-C₄)alkyl group where the indolyl moiety thereof is substituted with one or two substituents independently selected from halo, C₁-C₄

- 42 -

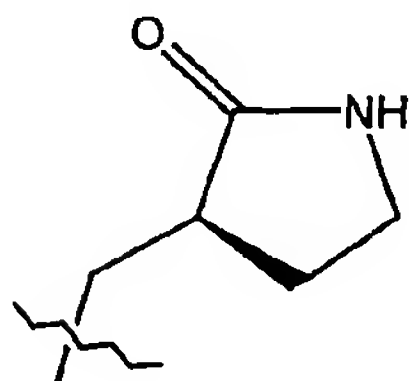
alkoxy, unsubstituted C₁-C₄ alkyl and C₁-C₄ haloalkyl, C₁-C₄ haloalkoxy, methylenedioxy, aryl, heterocycloalkyl, and heteroaryl where the aryl, heterocycloalkyl and heteroaryl is unsubstituted or substituted by one ore more substituents independently selected from halo, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy and methylenedioxy; and R^c is selected from -CH₂CH₂C(O)NH₂; -CH₂CH₂C(O)NH-alkyl; -CH₂NHC(O)CH₃;



and , where n is 1, when

R^a is (C₁-C₄)alkylcarbonyl-(C₁-C₄)alkyl, (C₃-C₈)cycloalkyl carbonyl-(C₁-C₄)alkyl, arylcarbonyl-(C₁-C₄)alkyl, heteroarylcarbonyl-(C₁-C₄)alkyl, (C₁-C₄)alkylcarbonylamino-(C₁-C₄)alkyl, C₃-C₈ cycloalkylcarbonylamino-(C₁-C₄)alkyl, heterocycloalkylcarbonylamino-(C₁-C₄)alkyl, arylcarbonylamino-(C₁-C₄)alkyl, heteroarylcarbonylamino-(C₁-C₄)alkyl, (C₁-C₄ alkylaminocarbonyl-(C₁-C₄)alkyl, (C₃-C₈)cycloalkylaminocarbonyl-(C₁-C₄)alkyl, heterocycloalkylaminocarbonyl-(C₁-C₄)alkyl, arylaminocarbonyl-(C₁-C₄)alkyl, heteroarylaminocarbonyl-(C₁-C₄)alkyl, wherein each (C₁-C₄)alkyl, (C₃-C₈)cycloalkyl, heterocycloalkyl, aryl and heteroaryl moiety thereof unsubstituted or substituted with one or more suitable substituents.

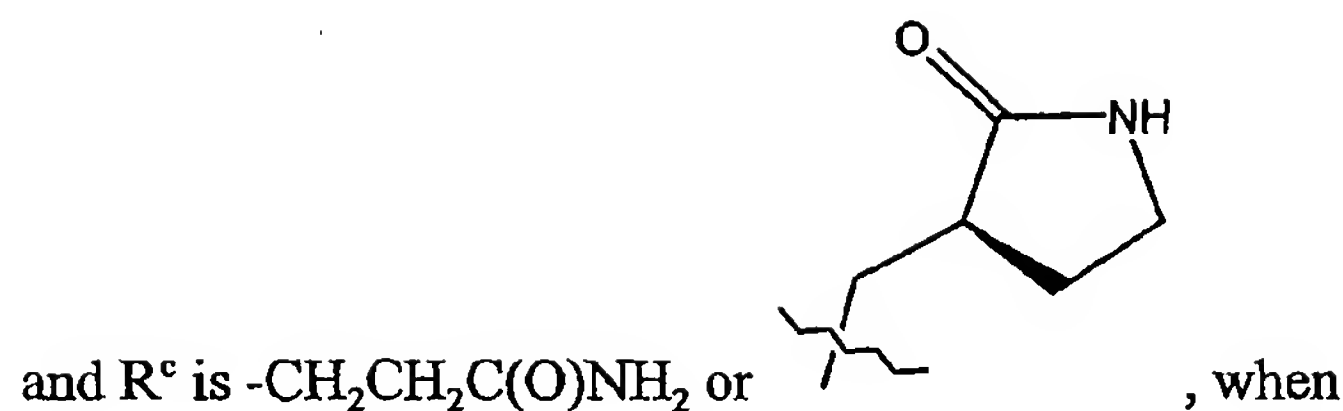
More preferably, in the compounds of Formula I, as defined above, R^c is



, when R^a is an indolylcarbonylamino-(C₁-C₄)alkyl group

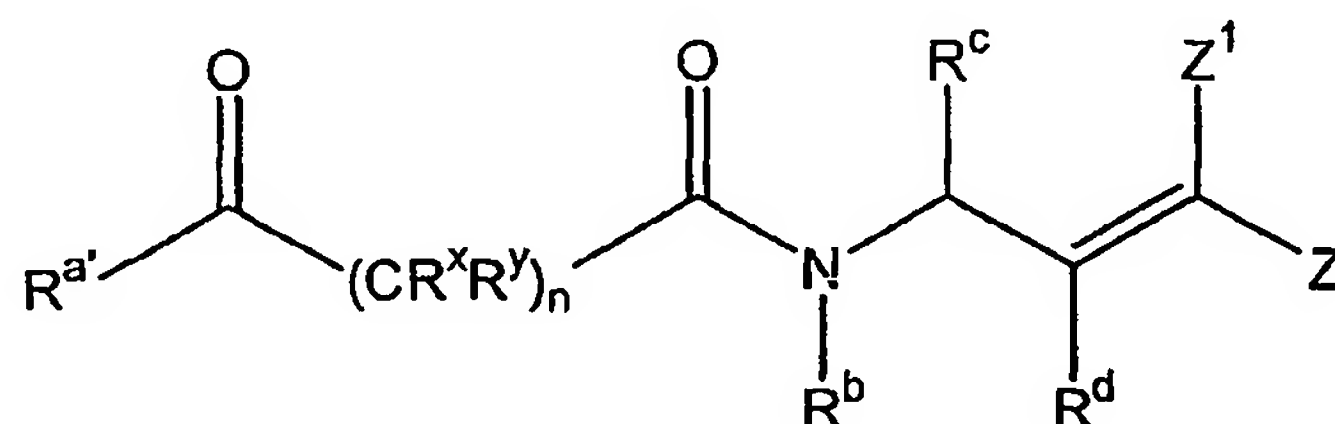
where the indolyl moiety thereof is substituted with one or two substituents independently selected from halo, C₁-C₄ alkoxy, unsubstituted C₁-C₄ alkyl and C₁-C₄ haloalkyl; and

- 43 -



R^a is (C₁-C₄)alkylcarbonyl-(C₁-C₄)alkyl, phenylcarbonyl-(C₁-C₄)alkyl, naphthylcarbonyl-(C₁-C₄)alkyl, pyrrolylcarbonyl-(C₁-C₄)alkyl, indolylcarbonyl-(C₁-C₄)alkyl, (C₁-C₄)alkylcarbonylamino-(C₁-C₄)alkyl, pyrrolylcarbonylamino-(C₁-C₄)alkyl, indolylcarbonylamino-(C₁-C₄)alkyl, phenylcarbonylamino-(C₁-C₄)alkyl, naphthylcarbonylamino-(C₁-C₄)alkyl, (C₁-C₄)alkylaminocarbonyl-(C₁-C₄)alkyl, phenylaminocarbonyl-(C₁-C₄)alkyl, naphthylaminocarbonyl-(C₁-C₄)alkyl, wherein each (C₁-C₄)alkyl, phenyl, naphthyl and pyrrolyl moiety thereof is group is unsubstituted or substituted with one or more substituents independently selected from halo, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, methylenedioxy, aryl, heterocycloalkyl, and heteroaryl, where the aryl, heterocycloalkyl and heteroaryl is unsubstituted or substituted by one ore more substituents independently selected from halo, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy and methylenedioxy; and said indolyl moiety is unsubstituted.

Other specific compounds of this invention have the formula:



II

20

R^{a'} is a (C₁-C₄)alkyl, (C₃-C₈)cycloalkyl, aryl or heteroaryl group, wherein the (C₁-C₄)alkyl, (C₃-C₈)cycloalkyl, aryl and heteroaryl group is unsubstituted or substituted with one or more substituents independently selected from (C₁-C₄)alkyl, aryl, (C₃-C₈)cycloalkyl, heterocycloalkyl, heteroaryl, halo, hydroxyl, (C₁-C₄)alkoxy,

- 44 -

alkylenedioxy (as a substituent for aryl or heteroaryl), aryloxy, (C₃-C₈)cycloalkoxy, heteroaryloxy, and carboxyl where the (C₁-C₄)alkyl, aryl, (C₃-C₈)cycloalkyl, heterocycloalkyl, heteroaryl moieties thereof are optionally substituted by one or more of (C₁-C₄)alkyl (except for alkyl), halo, (C₁-C₄)haloalkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkoxy, alkylenedioxy, aryl or heteroaryl, where the aryl or heteroaryl is unsubstituted or substituted with one or more substituents independently selected from alkyl, haloalkyl, alkylenedioxy, nitro, amino, hydroxamino, alkylamino, dialkylamino, halo, hydroxyl, alkoxy, haloalkoxy, aryloxy, mercapto, alkylthio or arylthio groups; preferably, R^a is a (C₁-C₄)alkyl, pyrrolyl, indolyl, phenyl or naphthyl group, where the (C₁-C₄)alkyl group is unsubstituted or substituted with one or more substituents independently selected from halo, C₁-C₄ alkoxy or C₁-C₄ haloalkoxy and the pyrrolyl, indolyl, phenyl or naphthyl group is unsubstituted or substituted with one or more substituents independently selected from halo, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, methylenedioxy, aryl, heterocycloalkyl and heteroaryl, where the aryl, heterocycloalkyl and heteroaryl is unsubstituted or substituted by one or more substituents independently selected from halo, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy and methylenedioxy; more preferably, R^a is an unsubstituted (C₁-C₄)alkyl, or a pyrrolyl, indolyl, phenyl or naphthyl group, where the pyrrolyl, indolyl, phenyl or naphthyl group is unsubstituted or substituted by one or more substituents independently selected from halo, C₁-C₄ alkyl, C₁-C₄ haloalkyl or a phenyl, naphthyl, isoxazolyl, pyridyl, quinoyl or isoquinoyl group, where the phenyl, naphthyl, isoxazolyl, pyridyl, quinoyl or isoquinoyl group is unsubstituted or substituted with one or more substituents independently selected from halo, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy and methylenedioxy; in specific embodiments, R^a is an unsubstituted (C₁-C₄)alkyl, pyrrolyl, indolyl, phenyl or naphthyl group or a pyrrolyl group substituted by phenyl, α -naphthyl, β -naphthyl, 2-chlorophenyl, 2- α,α,α -trifluoromethylphenyl, 3-chloro-6-methoxyphenyl, 2,3-dichlorophenyl, 4-isoquinoyl, 3-iso-propylphenyl, 2,5-dimethoxyphenyl, 2-methoxyphenyl, 2-methylphenyl (*o*-tolyl), 2-bromophenyl, 3-pyridyl, 4-pyridyl, 3-methyl-isoxazol-5-yl, 3,3,3-trifluoroprop-1-yl, or 2,3-benzo[d]dioxolyl or an indolyl

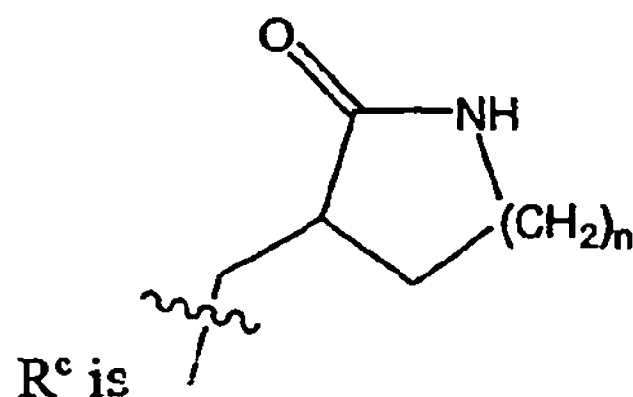
- 45 -

group substituted by halo, C₁-C₄ alkoxy, unsubstituted C₁-C₄ alkyl, C₁-C₄ haloalkyl, and C₁-C₄ alkoxyalkyl;

n is 1, 2 or 3; preferably n is 1 or 2; more preferably, n is 2;

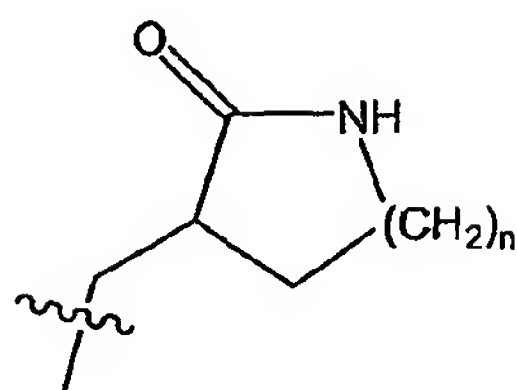
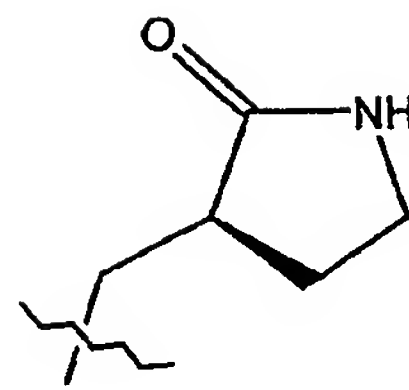
R^x is H and R^y is H, C₁-C₄ alkyl, C₁-C₄ haloalkyl or an arylalkyl,

5 heteroarylalkyl, cycloalkylalkyl group or a straight-chain saturated hydrocarbon moiety or an unsaturated hydrocarbon moiety, where the arylalkyl, heteroarylalkyl, cycloalkylalkyl group is unsubstituted or substituted with one or more suitable substituents; preferably, R^x is H and R^y is substituted or unsubstituted methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 10 2-propyn-1-yl, 3-methyl-3-buten-1-yl, -methylcyclohexyl, -methylthienyl or benzyl, where the substituted methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, and -methylcyclohexyl is substituted by one or more substituents independently selected from halo, alkoxy, aryloxy, alkylthio and arylthio; the substituted thienyl is substituted 15 by one or more substituents independently selected from lower alkyl, lower alkoxy, hydroxy, amino, alkylamino, dialkylamino and halo; and the phenyl moiety of the substituted benzyl is substituted by one or more substituents independently selected from lower alkyl, lower alkoxy, alkylenedioxy, hydroxy, amino, alkylamino, dialkylamino and halo; more preferably, R^x is H and R^y is ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl, 20 3-methyl-3-buten-1-yl, -methylcyclohexyl, benzyl or substituted benzyl, wherein the phenyl moiety of the substituted benzyl comprises one or more substituents independently selected from C₁-C₄ alkyl, C₁-C₄ alkoxy and halo; even more preferably, where R^x is H and R^y is H, ethyl, 2-propyn-1-yl, methylcyclohexyl or benzyl;



, where n is 1 or 2; preferably R^c is

- 46 -

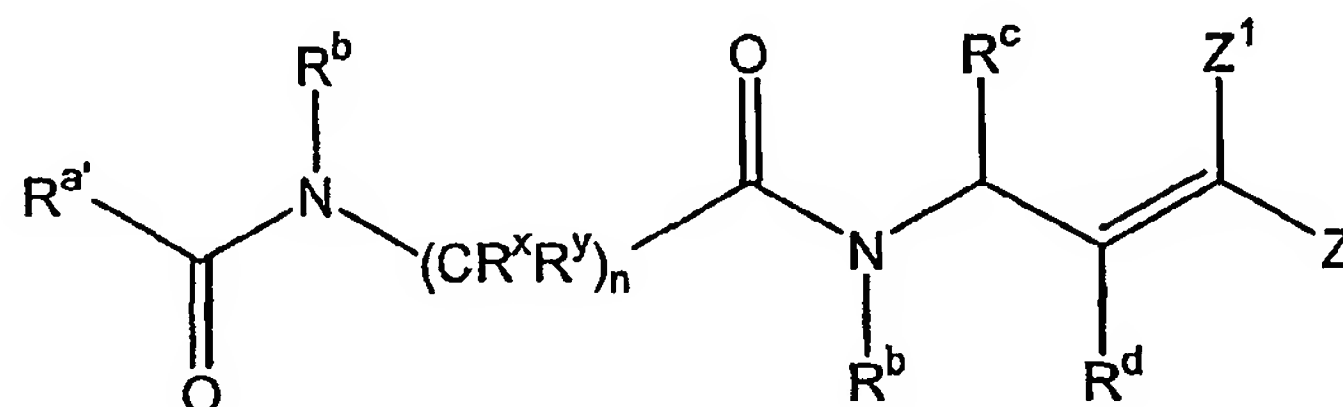
where n is 1; more preferably, R^c is

; and

R^b, R^d, Z and Z¹ are defined as in Formula I, above.

Yet other specific compounds of this invention have the formula:

5



III

wherein:

10

R^{a'} is a (C₁-C₄)alkyl, (C₃-C₈)cycloalkyl, aryl or heteroaryl group, wherein the (C₁-C₄)alkyl, (C₃-C₈)cycloalkyl, aryl and heteroaryl group is unsubstituted or substituted with one or more suitable substituents provided that R^{a'} is not an amino-

substituted (C₁-C₄)alkyl group; preferably, R^{a'} is a (C₁-C₄)alkyl, phenyl, naphthyl, pyrrolyl or indolyl group, where the (C₁-C₄)alkyl group is unsubstituted or substituted

15

with one or more substituents independently selected from halo, C₁-C₄ alkoxy or C₁-C₄

haloalkoxy and the phenyl, naphthyl, pyrrolyl or indolyl group is unsubstituted or

substituted with one or more substituents independently selected from halo, C₁-C₄

alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, methylenedioxy, aryl,

heterocycloalkyl, and heteroaryl, where the aryl, heterocycloalkyl or heteroaryl is

20

unsubstituted or substituted by one or more substituents independently selected from

halo, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy and

methylenedioxy; more preferably, R^{a'} is a pyrrolyl or indolyl group, where the pyrrolyl

or indolyl group is unsubstituted or substituted by one or more substituents

independently selected from halo, C₁-C₄ alkyl, C₁-C₄ haloalkyl or a phenyl, naphthyl,

25

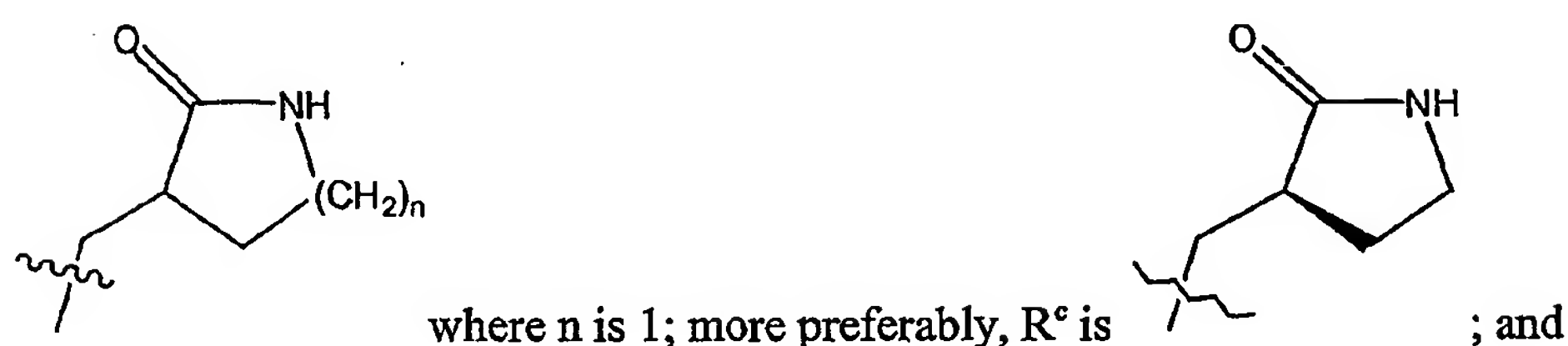
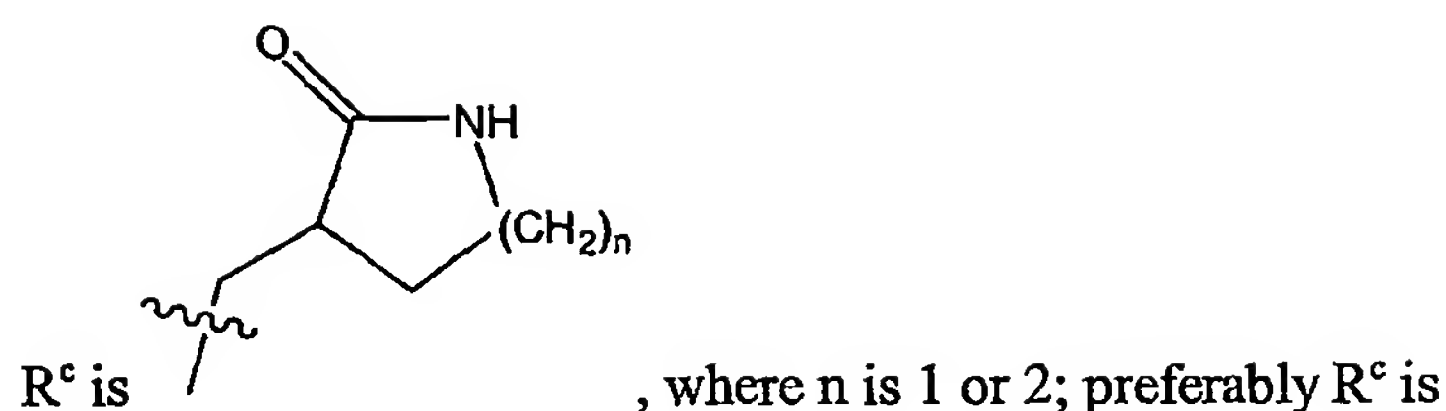
isoxazolyl, pyridyl, quinoyl or isoquinoyl group, where the phenyl, naphthyl,

isoxazolyl, pyridyl, quinoyl or isoquinoyl group is unsubstituted or substituted with

- 47 -

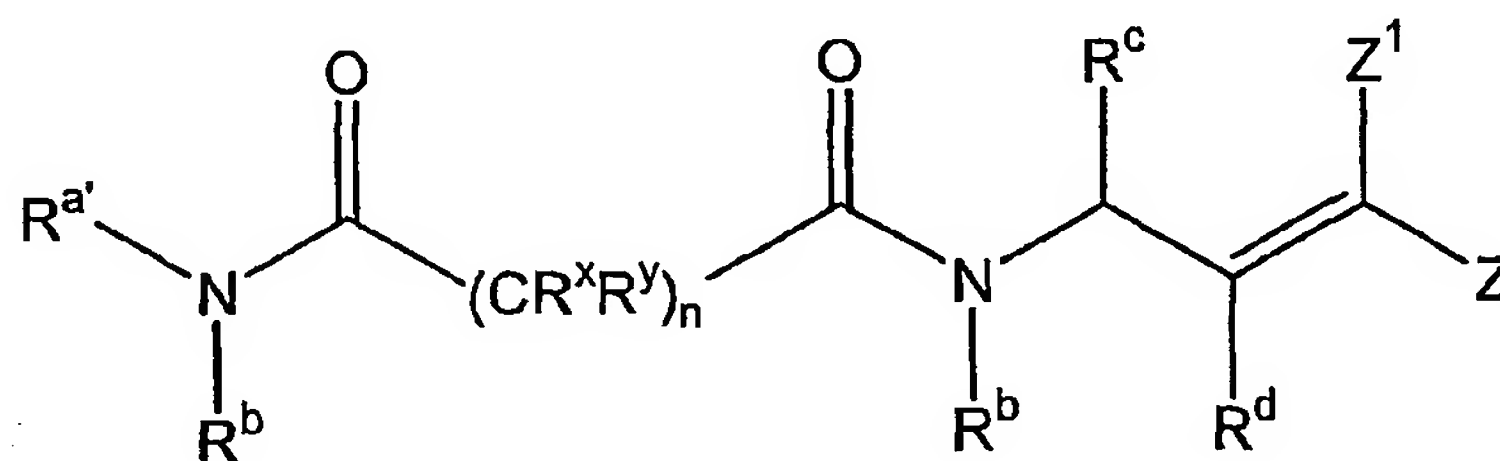
- one or more substituents independently selected from halo, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy and methylenedioxy; even more preferably, R^a is a pyrrolyl group that is unsubstituted or substituted by phenyl, α-naphthyl, β-naphthyl, 2-chlorophenyl, 2-α,α,α-trifluoromethylphenyl, 3-chloro-6-methoxyphenyl, 2,3-dichlorophenyl, 4-isoquinoyl, 3-iso-propylphenyl, 2,5-dimethoxyphenyl, 2-methoxyphenyl, 2-methylphenyl (o-tolyl), 2-bromophenyl, 3-pyridyl, 4-pyridyl, 3-methyl-isoxazol-5-yl, 3,3,3-trifluoroprop-1-yl, or 2,3-benzo[d]dioxolyl;
- n is 1, 2 or 3; preferably n is 1;
- R^x is H and R^y is H, C₁-C₄ alkyl, C₁-C₄ haloalkyl or an arylalkyl, heteroarylalkyl, cycloalkylalkyl group or a straight-chain saturated hydrocarbon moiety or an unsaturated hydrocarbon moiety, where the arylalkyl, heteroarylalkyl, cycloalkylalkyl group is unsubstituted or substituted with one or more suitable substituents; preferably, R^x is H and R^y is substituted or unsubstituted methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, -methylcyclohexyl, -methylthienyl or benzyl, where the substituted methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, and -methylcyclohexyl is substituted by one or more substituents independently selected from halo, alkoxy, aryloxy, alkylthio and arylthio; the substituted thienyl is substituted by one or more substituents independently selected from lower alkyl, lower alkoxy, hydroxy, amino, alkylamino, dialkylamino and halo; and the phenyl moiety of the substituted benzyl is substituted by one or more substituents independently selected from lower alkyl, lower alkoxy, alkylendioxy, hydroxy, amino, alkylamino, dialkylamino and halo; more preferably, R^x is H and R^y is ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, -methylcyclohexyl, benzyl or substituted benzyl, wherein the phenyl moiety of the substituted benzyl comprises one or more substituents independently selected from C₁-C₄ alkyl, C₁-C₄ alkoxy and halo; even more preferably, where R^x is H and R^y is H, ethyl, 2-propyn-1-yl, methylcyclohexyl or benzyl;

- 48 -



5 R^b , R^d , Z and Z^1 are defined as in Formula I, above.

Another embodiment of this invention comprises compounds having the formula:



10

IV

wherein:

$\text{R}^{a'}$ is a $(\text{C}_1\text{-C}_4)$ alkyl, $(\text{C}_3\text{-C}_8)$ cycloalkyl, heterocycloalkyl, aryl or heteroaryl group, wherein the $(\text{C}_1\text{-C}_4)$ alkyl, $(\text{C}_3\text{-C}_8)$ cycloalkyl, heterocycloalkyl, aryl and heteroaryl group is unsubstituted or substituted with one or more suitable substituents; preferably, $\text{R}^{a'}$ is a $(\text{C}_1\text{-C}_4)$ alkyl, phenyl or naphthyl group, where the $(\text{C}_1\text{-C}_4)$ alkyl group is unsubstituted or substituted with one or more substituents independently selected from halo, $\text{C}_1\text{-C}_4$ alkoxy or $\text{C}_1\text{-C}_4$ haloalkoxy and the phenyl or naphthyl group is unsubstituted or substituted with one or more substituents independently selected from halo, $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_1\text{-C}_4$ haloalkyl, $\text{C}_1\text{-C}_4$ alkoxy, $\text{C}_1\text{-C}_4$ haloalkoxy, methylenedioxy and phenyl, where the phenyl is unsubstituted or substituted by one or more substituents independently selected from halo, $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_1\text{-C}_4$ haloalkyl, $\text{C}_1\text{-C}_4$ alkoxy, $\text{C}_1\text{-C}_4$ haloalkoxy and methylenedioxy; in specific embodiments, $\text{R}^{a'}$ is a halo-substituted phenyl group;

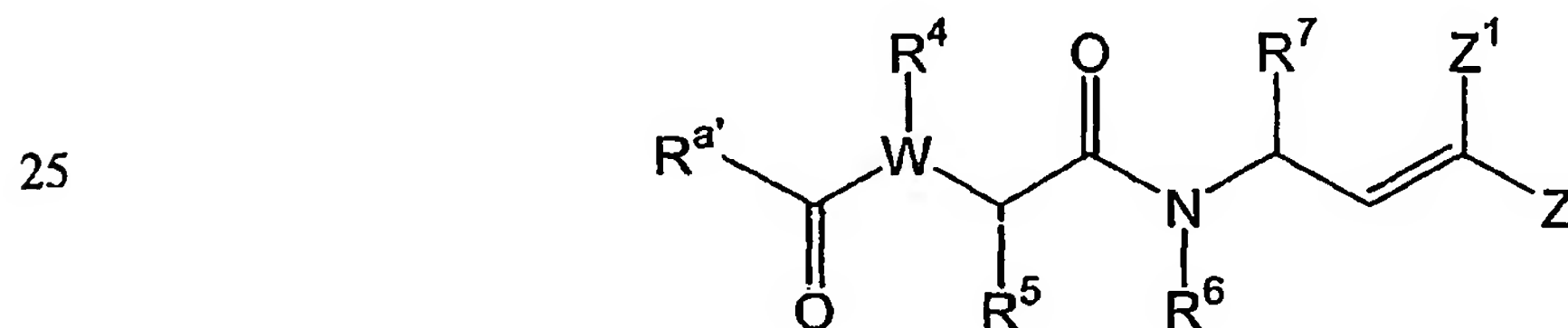
20

n is 1, 2 or 3; preferably, n is 1 or 2; more preferably, n is 1;

- 49 -

R^x is H and R^y is H, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl or an arylalkyl, heteroarylalkyl, cycloalkylalkyl group or a straight-chain saturated hydrocarbon moiety or an unsaturated hydrocarbon moiety, where the arylalkyl, heteroarylalkyl, cycloalkylalkyl group is unsubstituted or substituted with one or more suitable substituents; preferably, R^x is H and R^y is substituted or unsubstituted methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, -methylcyclohexyl, -methylthienyl or benzyl, where the substituted methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, and -methylcyclohexyl is substituted by one or more substituents independently selected from halo, alkoxy, aryloxy, alkylthio and arylthio; the substituted thienyl is substituted by one or more substituents independently selected from lower alkyl, lower alkoxy, hydroxy, amino, alkylamino, dialkylamino and halo; and the phenyl moiety of the substituted benzyl is substituted by one or more substituents independently selected from lower alkyl, lower alkoxy, alkylendioxy, hydroxy, amino, alkylamino, dialkylamino and halo; more preferably, R^x is H and R^y is ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, -methylcyclohexyl, benzyl or substituted benzyl, wherein the phenyl moiety of the substituted benzyl comprises one or more substituents independently selected from C_1 - C_4 alkyl, C_1 - C_4 alkoxy and halo; even more preferably, where R^x is H and R^y is H, ethyl, 2-propyn-1-yl, methylcyclohexyl or benzyl; and and R^b , R^c , R^d , Z and Z^1 are defined as in Formula I, above.

Other specific embodiments of this invention comprise the compounds having the formula:



VI

wherein:

W is CH or N;

- 50 -

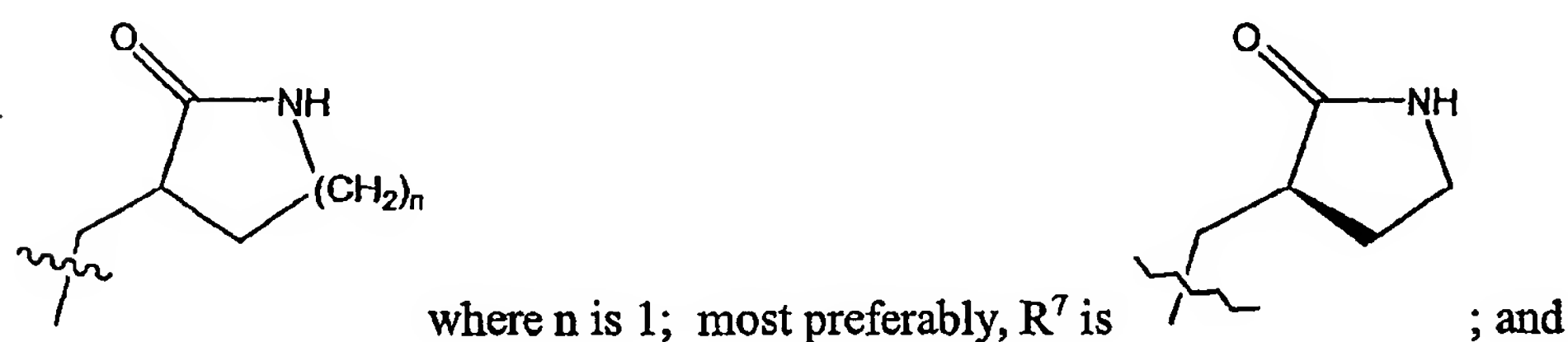
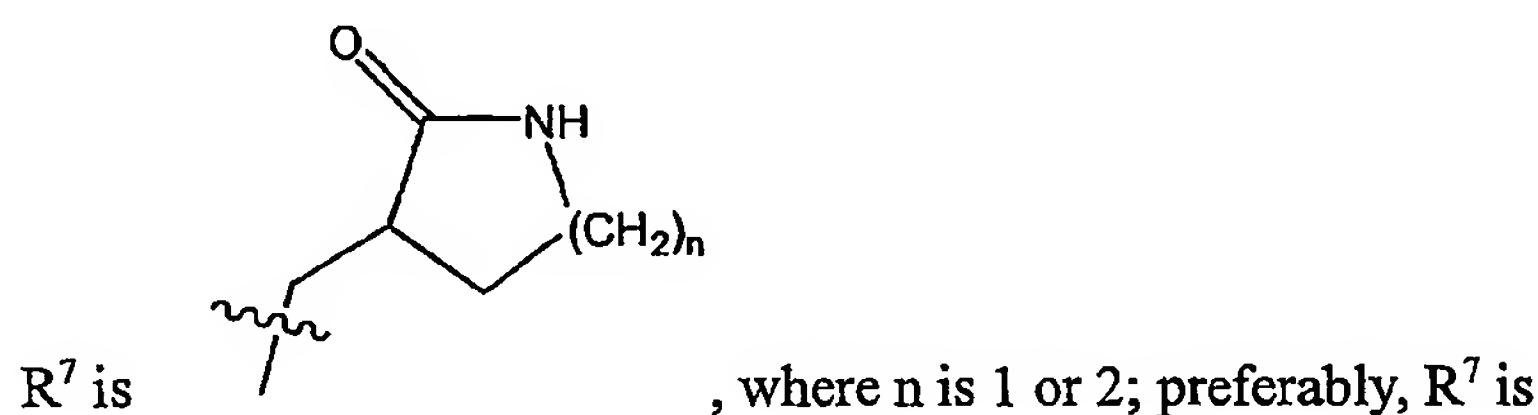
R^a is a C₁-C₄ alkyl, C₃-C₈ cycloalkyl, aryl or heteroaryl group, where the C₁-C₄ alkyl, C₃-C₈ cycloalkyl, aryl, and heteroaryl group is unsubstituted or substituted with one or more suitable substituents, provided that R^a is not an amino-substituted alkyl group; preferably, R^a is a C₁-C₄ alkyl, C₅-C₆ cycloalkyl, phenyl, naphthyl or heteroaryl group; where the phenyl, naphthyl or heteroaryl group is unsubstituted or substituted with one or more substituents independently selected from halo, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, methylenedioxy, aryl, heterocycloalkyl, and heteroaryl, where the aryl, heterocycloalkyl and heteroaryl is unsubstituted or substituted by one or more substituents independently selected from halo, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy and methylenedioxy; more preferably, R^a is a C₁-C₄ alkyl, C₅-C₆ cycloalkyl, phenyl, naphthyl, pyrrolyl or indolyl, group, where the phenyl, naphthyl, pyrrolyl or indolyl, group is unsubstituted or substituted with one or more substituents independently selected from halo, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, methylenedioxy and a phenyl, naphthyl, isoquinoyl, pyridyl or isoxazolyl group, wherein the phenyl, naphthyl, isoquinoyl, pyridyl and isoxazolyl group is unsubstituted or substituted by one or more substituents independently selected from halo, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy and methylenedioxy;

R⁴ and R⁶ are each independently H or C₁-C₄ alkyl; preferably R⁴ and R⁶ are each H;

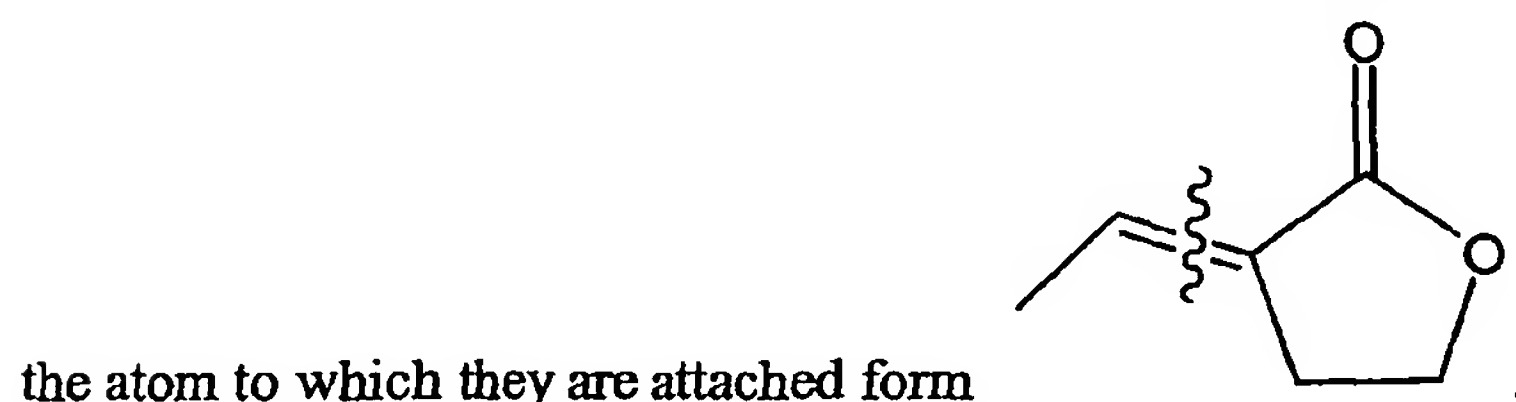
R⁵ is H, C₁-C₄ alkyl, C₁-C₄ haloalkyl or an arylalkyl, heteroarylalkyl, cycloalkylalkyl group or a straight-chain saturated hydrocarbon moiety or an unsaturated hydrocarbon moiety, where the arylalkyl, heteroarylalkyl, cycloalkylalkyl group is unsubstituted or substituted with one or more suitable substituents; preferably, R⁵ is H or substituted or unsubstituted methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, -methylcyclohexyl, -methylthienyl or benzyl, where the substituted methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, and -methylcyclohexyl is substituted by one or more substituents independently selected from halo, alkoxy, aryloxy, alkylthio and arylthio; the substituted thienyl is substituted

- 51 -

by one or more substituents independently selected from lower alkyl, lower alkoxy, hydroxy, amino, alkylamino, dialkylamino and halo; and the phenyl moiety of the substituted benzyl is substituted by one or more substituents independently selected from lower alkyl, lower alkoxy, alkylendioxy, hydroxy, amino, alkylamino, dialkylamino and halo; more preferably, R^5 is H, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, -methylcyclohexyl, benzyl or substituted benzyl, wherein the phenyl moiety of the substituted benzyl comprises one or more substituents independently selected from C_1 - C_4 alkyl, C_1 - C_4 alkoxy and halo; even more preferably, R^5 is H, ethyl, 2-propyn-1-yl, methylcyclohexyl or benzyl;



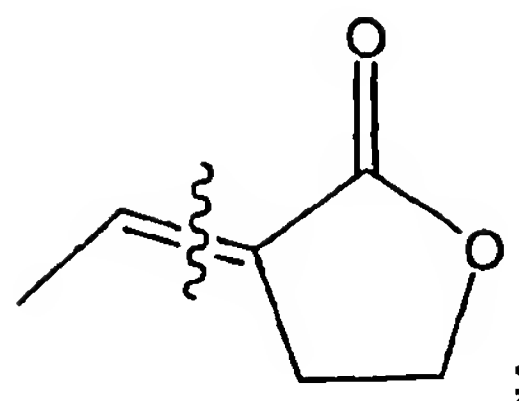
Z^1 is H or C_1 - C_4 alkyl and Z is $-CO_2$ -alkyl, $-CO_2$ -cycloalkyl, $-CO_2$ -alkylaryl or $-CO_2$ -alkylheterocycloaryl, or Z^1 and Z taken together with



preferably, Z^1 is H and Z is $-CO_2CH_2CH_3$, $-CO_2(CH(CH_3)_2)$, $-CO_2(C(CH_3)_3)$, $-CO_2CH_2(C(CH_3)_3)$, $-CO_2$ (cyclo- C_5H_9) or Z^1 and Z taken together with the atom

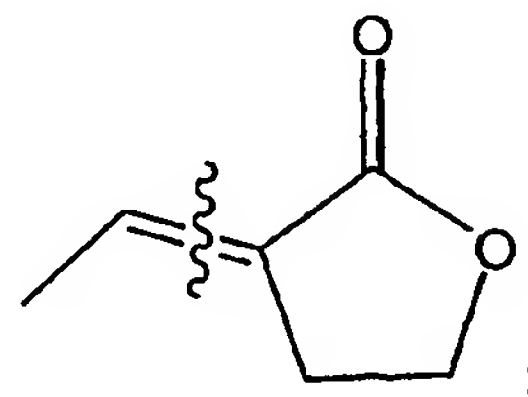
- 52 -

to which they are attached form



most preferably, Z^1 is H and Z is $-\text{CO}_2\text{CH}_2\text{CH}_3$ or Z^1 and Z taken together

with the atom to which they are attached form

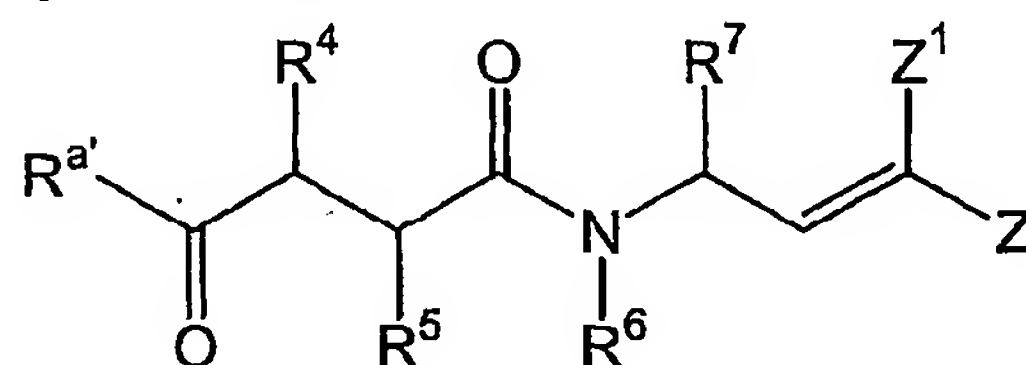


5

or a prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate of said compound.

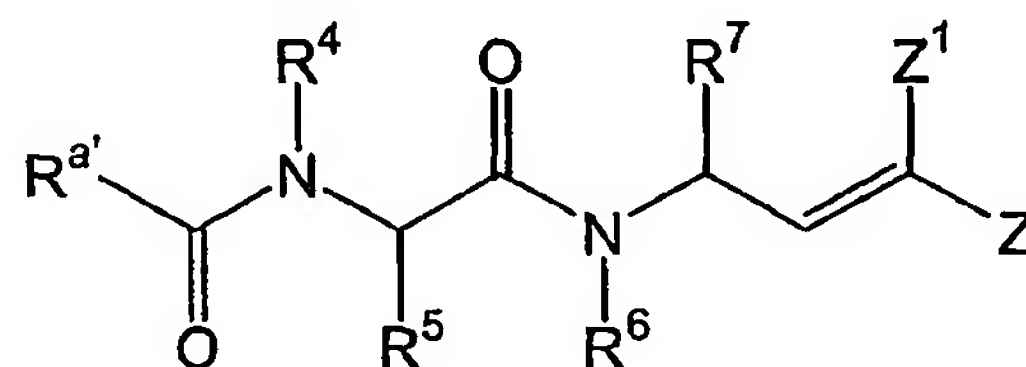
Specific embodiments of Formula VI of this invention comprise the

10 compounds depicted by the formula:



VII

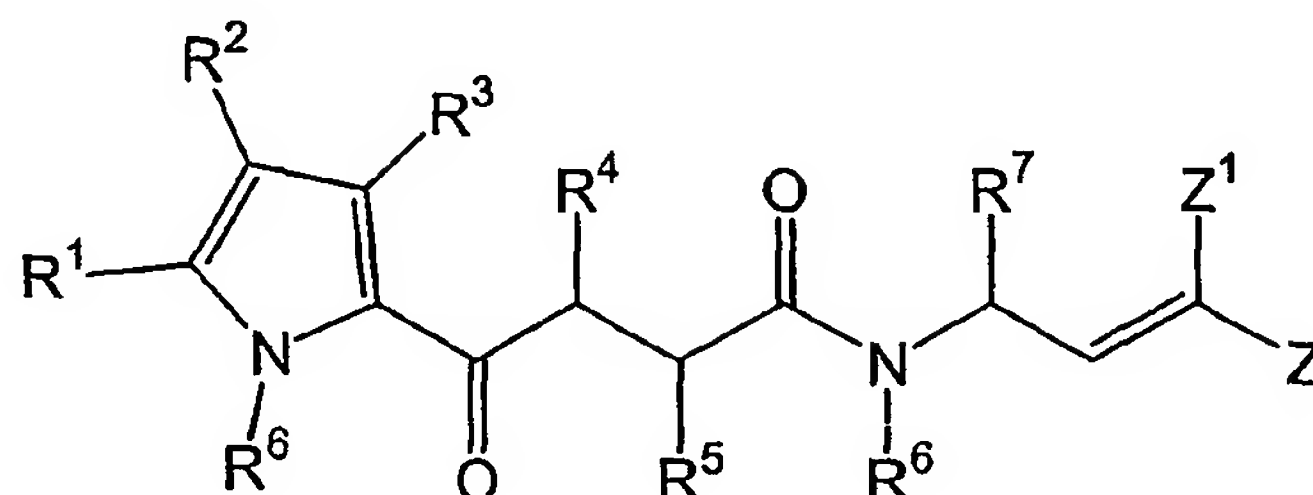
15 and the compounds depicted by the formula:



VIII

20 wherein R^a , R^4 , R^5 , R^6 , R^7 , Z and Z^1 are as defined above.

In addition, specific embodiments of this invention comprise the compounds depicted by the formula:



IX

wherein:

R^1 is H, halo, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, or an aryl or heteroaryl group, where the aryl or heteroaryl group is unsubstituted or substituted with one or more suitable substituents; preferably, R^1 is H, halo, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl or a phenyl, naphthyl, isoxazolyl, pyridyl, quinoyl or isoquinoyl group, where the phenyl, naphthyl, isoxazolyl, pyridyl, quinoyl or isoquinoyl group is unsubstituted or substituted with one or more substituents independently selected from: halo, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy and methylenedioxy; more preferably, R^1 is H, phenyl, α -naphthyl, β -naphthyl, 2-chlorophenyl, 2- α,α,α -trifluoromethylphenyl, 3-chloro-6-methoxyphenyl, 2,3-dichlorophenyl, 4-isoquinoyl, 3-iso-propylphenyl, 2,5-dimethoxyphenyl, 2-methoxyphenyl, 2-methylphenyl (o-tolyl), 2-bromophenyl, 3-pyridyl, 4-pyridyl, 3-methyl-isoxazol-5-yl, 3,3,3-trifluoroprop-1-yl, or 2,3-benzo[d]dioxolyl;

R^2 and R^3 are each independently H or C_1 - C_4 alkyl; preferably R^2 and R^3 are each H; or

R^1 together with R^2 form a cycloalkyl, heterocycloalkyl, aryl or heteroaryl ring, where the cycloalkyl, heterocycloalkyl, aryl or heteroaryl ring is unsubstituted or substituted with one or more suitable substituents; or preferably, R^1 together with R^2 form a phenyl ring, which is unsubstituted or substituted with one or more suitable substituents and R^3 is H;

R^4 and R^6 are each independently H or C_1 - C_4 alkyl; preferably R^4 and R^6 are each H;

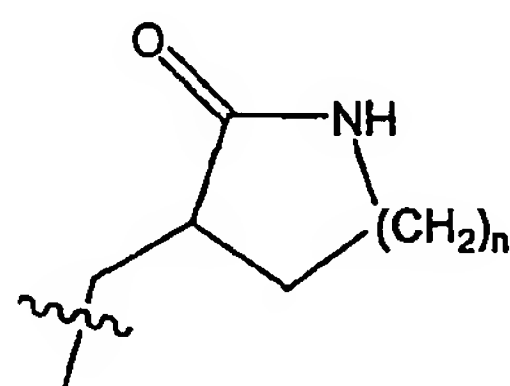
- 54 -

R^5 is H, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl or an arylalkyl, heteroarylalkyl, cycloalkylalkyl group or a straight-chain saturated hydrocarbon moiety or an unsaturated hydrocarbon moiety, where the arylalkyl, heteroarylalkyl, cycloalkylalkyl group is unsubstituted or substituted with one or more suitable substituents; preferably,

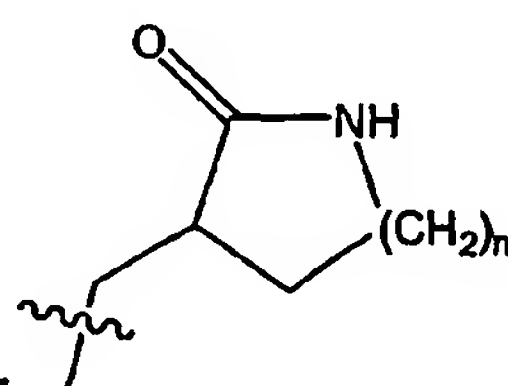
R^5 is H or substituted or unsubstituted methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, -methylcyclohexyl, -methylthienyl or benzyl, where the substituted methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, and -methylcyclohexyl is substituted by one or more substituents independently selected from halo, alkoxy, aryloxy, alkylthio and arylthio; the substituted thienyl is substituted by one or more substituents independently selected from lower alkyl, lower alkoxy, hydroxy, amino, alkylamino, dialkylamino and halo; and the phenyl moiety of the substituted benzyl is substituted by one or more substituents independently selected from lower alkyl, lower alkoxy, alkylenedioxy, hydroxy, amino, alkylamino, dialkylamino and halo; more preferably, R^5 is H, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, -methylcyclohexyl, benzyl or substituted benzyl, wherein the phenyl moiety of the substituted benzyl comprises one or more substituents independently selected from C_1 - C_4 alkyl, C_1 - C_4 alkoxy and halo; even more preferably, R^5 is H, ethyl, 2-propyn-1-yl, methylcyclohexyl or benzyl;

R^7 is selected from $-CH_2CH_2C(O)NH_2$; $-CH_2CH_2C(O)NH$ -alkyl;

$-CH_2NHC(O)CH_3$; and

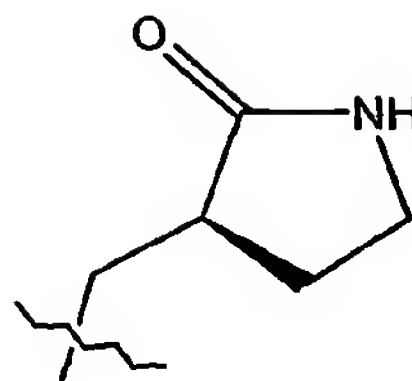


, where n is 1 or 2;



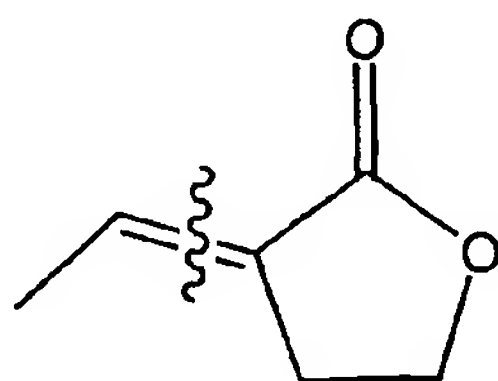
preferably, R^7 is $-CH_2CH_2C(O)NH_2$ or $-CH_2CH_2C(O)NH$ -alkyl, where n is 1;

- 55 -



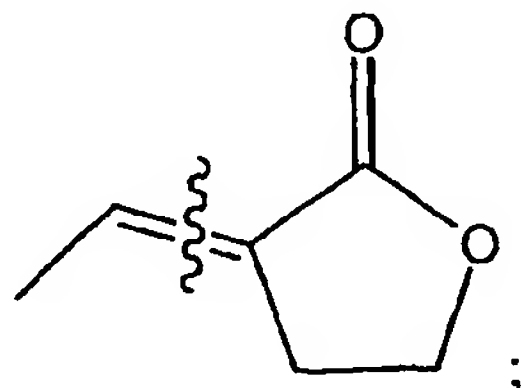
most preferably, R^7 is $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$ or ; and

Z^1 is H or $\text{C}_1\text{-C}_4$ alkyl and Z is $-\text{CO}_2\text{-alkyl}$, $-\text{CO}_2\text{-cycloalkyl}$, $-\text{CO}_2\text{-alkylaryl}$ or $-\text{CO}_2\text{-alkylheterocycloaryl}$, or Z^1 and Z taken together with the atom to which



5 they are attached form , preferably, Z^1 is H and

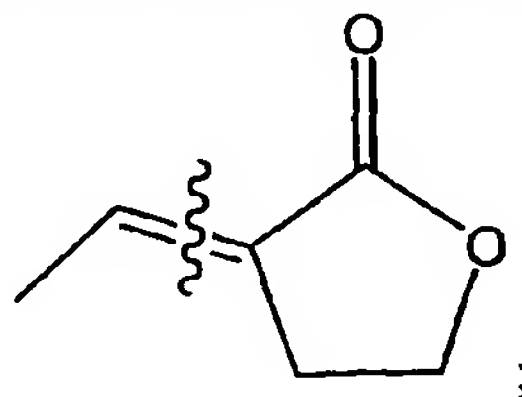
Z is $-\text{CO}_2\text{CH}_2\text{CH}_3$, $-\text{CO}_2(\text{CH}(\text{CH}_3)_2)$, $-\text{CO}_2(\text{C}(\text{CH}_3)_3)$, $-\text{CO}_2\text{CH}_2(\text{C}(\text{CH}_3)_3)$, $-\text{CO}_2(\text{cyclo-C}_5\text{H}_9)$ or Z^1 and Z taken together with the atom to which they



are attached form ;

10

most preferably, Z^1 is H and Z is $-\text{CO}_2\text{CH}_2\text{CH}_3$ or Z^1 and Z taken together with the



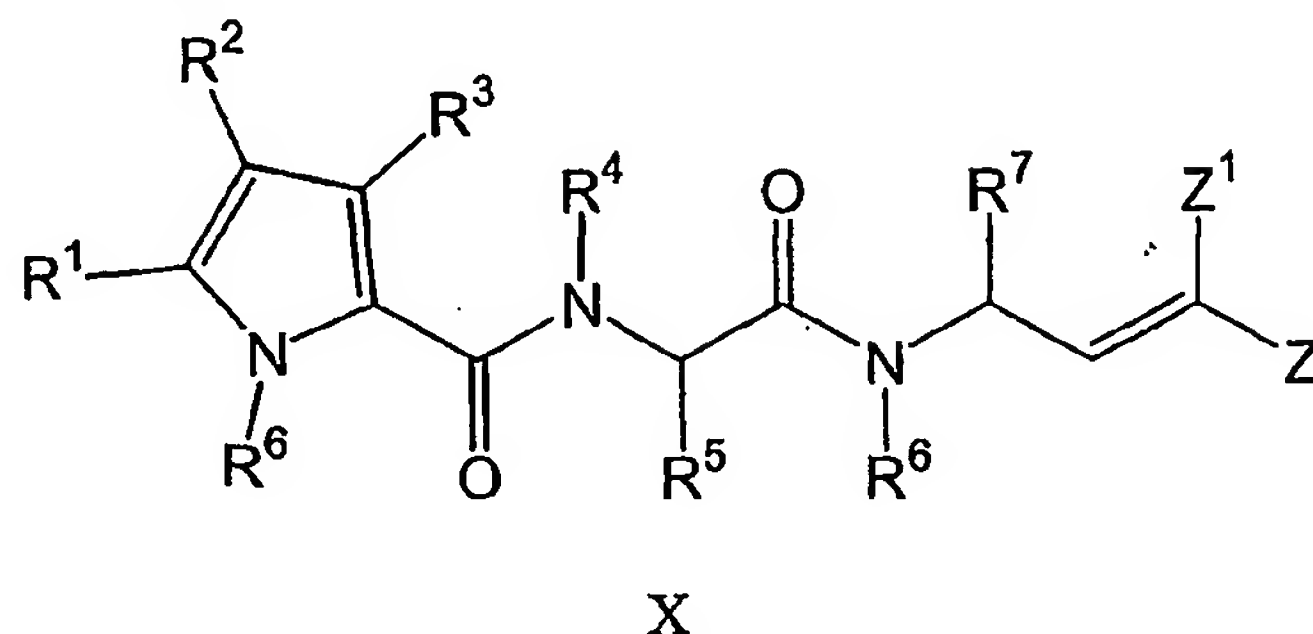
atom to which they are attached form ;

15

or a prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate of said compound.

- 56 -

Another specific embodiment of this invention comprises the compounds depicted by the formula:



5

wherein:

R^1 is H, halo, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, or an aryl or heteroaryl group, where the aryl or heteroaryl group is unsubstituted or substituted with one or more suitable substituents; preferably, R^1 is H, halo, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl or a phenyl, naphthyl, isoxazolyl, pyridyl, quinoyl or isoquinoyl group, where the phenyl, naphthyl, isoxazolyl, pyridyl, quinoyl or isoquinoyl group is unsubstituted or substituted with one or more substituents independently selected from: halo, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy and methylenedioxy; more preferably, R^1 is H, phenyl, α -naphthyl, β -naphthyl, 2-chlorophenyl, 2- α,α,α -trifluoromethylphenyl, 3-chloro-6-methoxyphenyl, 2,3-dichlorophenyl, 4-isoquinoyl, 3-iso-propylphenyl, 2,5-dimethoxyphenyl, 2-methoxyphenyl, 2-methylphenyl (o-tolyl), 2-bromophenyl, 3-pyridyl, 4-pyridyl, 3-methyl-isoxazol-5-yl, 3,3,3-trifluoroprop-1-yl, or 2,3-benzo[d]dioxolyl;

R^2 and R^3 are each independently H or C_1 - C_4 alkyl; preferably R^2 and R^3 are each H; or

R^1 together with R^2 form a cycloalkyl, heterocycloalkyl, aryl or heteroaryl ring, where the cycloalkyl, heterocycloalkyl, aryl or heteroaryl ring is unsubstituted or substituted with one or more suitable substituents; or preferably, R^1 together with R^2 form an unsubstituted phenyl ring and R^3 is H;

R^4 and R^6 are each independently H or C_1 - C_4 alkyl; preferably R^4 and R^6 are each H;

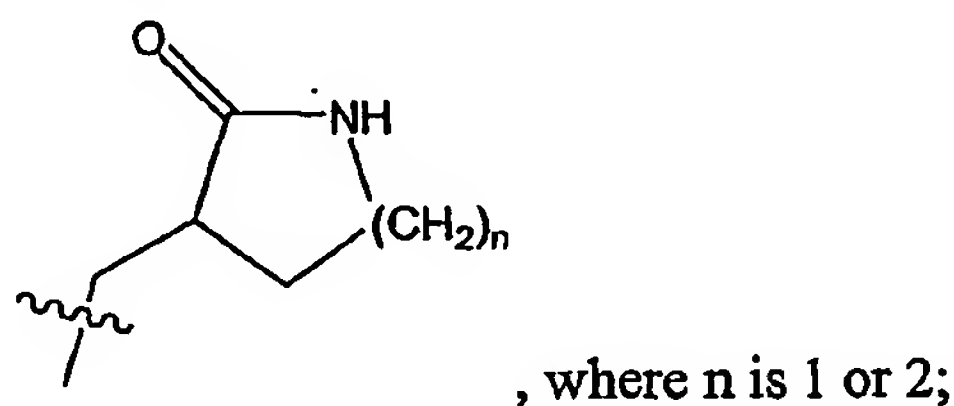
R^5 is H, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl or an arylalkyl, heteroarylalkyl, cycloalkylalkyl group or a straight-chain saturated hydrocarbon moiety or an

- 57 -

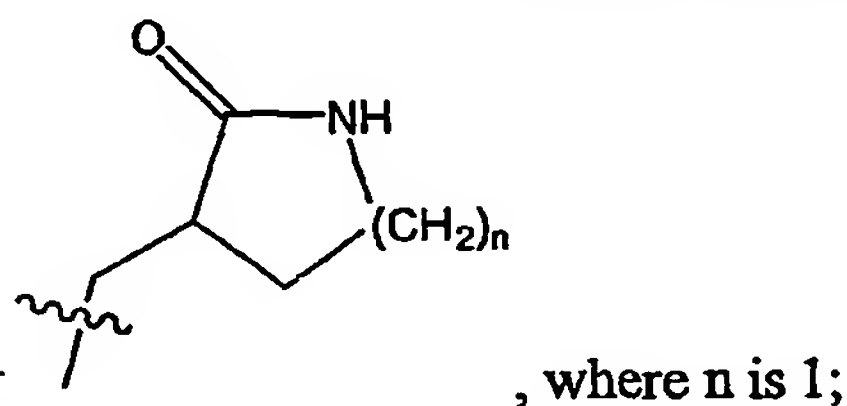
unsaturated hydrocarbon moiety, where the arylalkyl, heteroarylalkyl, cycloalkylalkyl group is unsubstituted or substituted with one or more suitable substituents; preferably, R^5 is H or substituted or unsubstituted methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, -methylcyclohexyl, -methylthienyl or benzyl, where the substituted methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, and -methylcyclohexyl is substituted by one or more substituents independently selected from halo, alkoxy, aryloxy, alkylthio and arylthio; the substituted thienyl is substituted by one or more substituents independently selected from lower alkyl, lower alkoxy, hydroxy, amino, alkylamino, dialkylamino and halo; and the phenyl moiety of the substituted benzyl is substituted by one or more substituents independently selected from lower alkyl, lower alkoxy, alkylenedioxy, hydroxy, amino, alkylamino, dialkylamino and halo; more preferably, R^5 is H, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, -methylcyclohexyl, benzyl or substituted benzyl, wherein the phenyl moiety of the substituted benzyl comprises one or more substituents independently selected from C_1 - C_4 alkyl, C_1 - C_4 alkoxy and halo; even more preferably, R^5 is H, ethyl, 2-propyn-1-yl, methylcyclohexyl or benzyl;

R^7 is selected from $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$; $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH-alkyl}$;

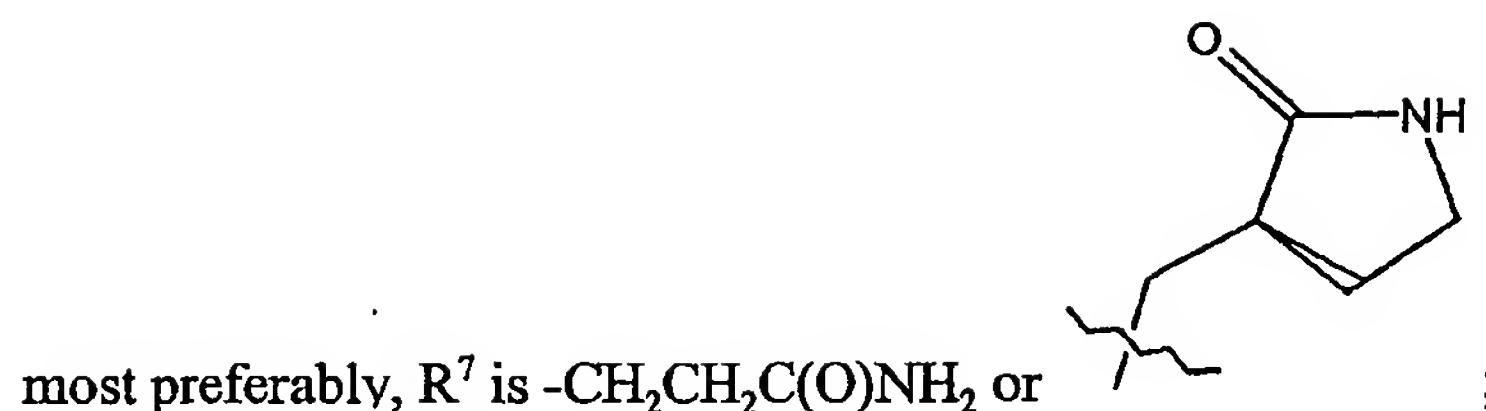
$-\text{CH}_2\text{NHC}(\text{O})\text{CH}_3$; and



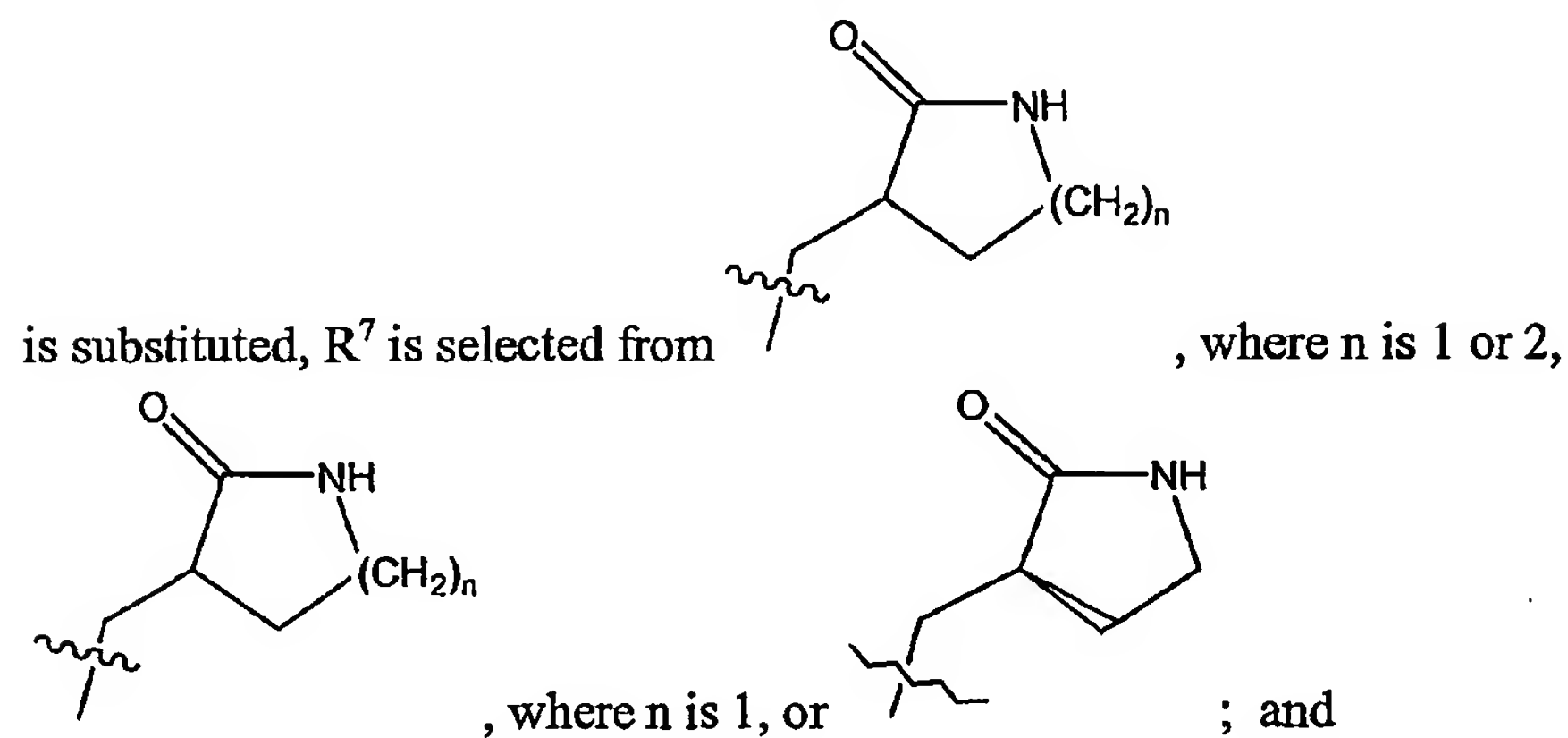
preferably, R^7 is $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$ or



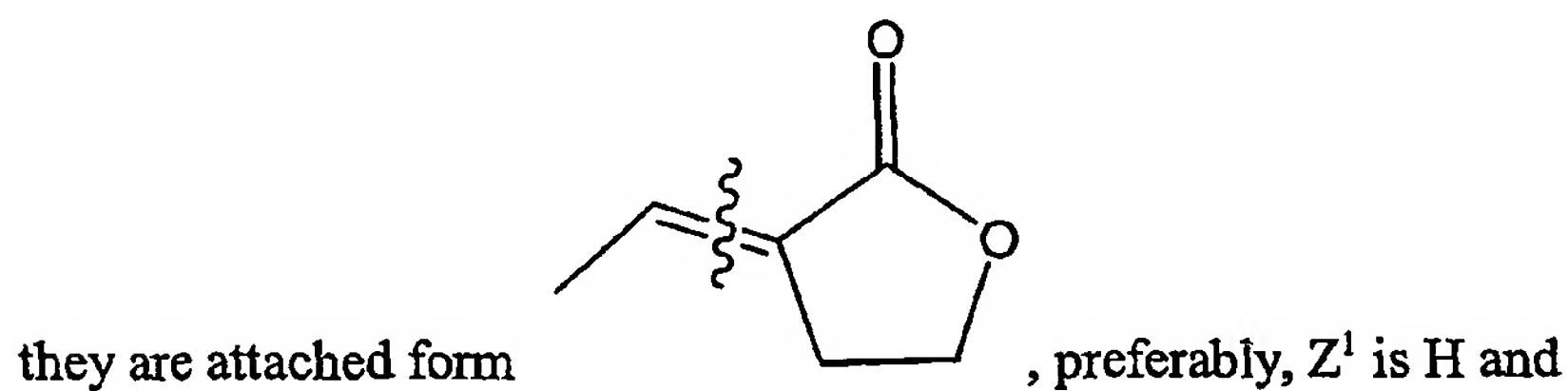
- 58 -



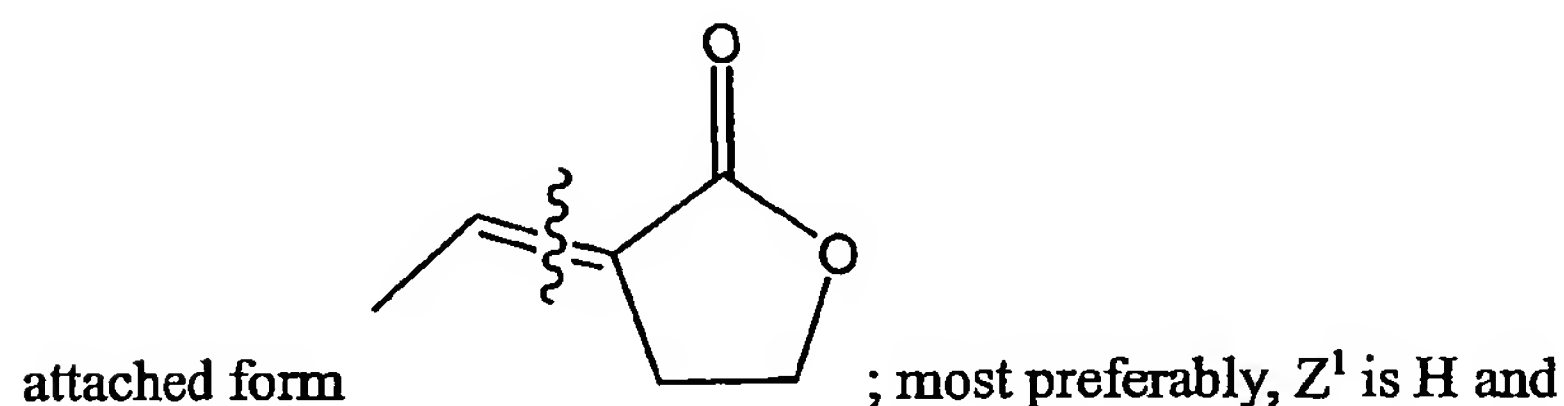
provided that when R^1 together with R^2 form a phenyl ring and the phenyl ring



Z^1 is H or $\text{C}_1\text{-C}_4$ alkyl and Z is $-\text{CO}_2\text{-alkyl}$, $-\text{CO}_2\text{-cycloalkyl}$, $-\text{CO}_2\text{-alkylaryl}$ or $-\text{CO}_2\text{-alkylheterocycloaryl}$, or Z^1 and Z taken together with the atom to which

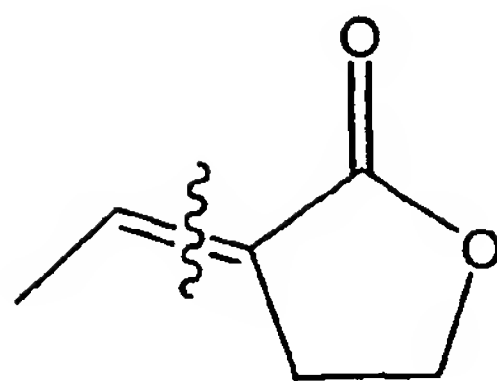


Z is $-\text{CO}_2\text{CH}_2\text{CH}_3$, $-\text{CO}_2(\text{CH}(\text{CH}_3)_2)$, $-\text{CO}_2(\text{C}(\text{CH}_3)_3)$, $-\text{CO}_2\text{CH}_2(\text{C}(\text{CH}_3)_3)$, $-\text{CO}_2(\text{cyclo-C}_5\text{H}_9)$ or Z^1 and Z taken together with the atom to which they are



Z is $-\text{CO}_2\text{CH}_2\text{CH}_3$ or Z^1 and Z taken together with the atom to which they are

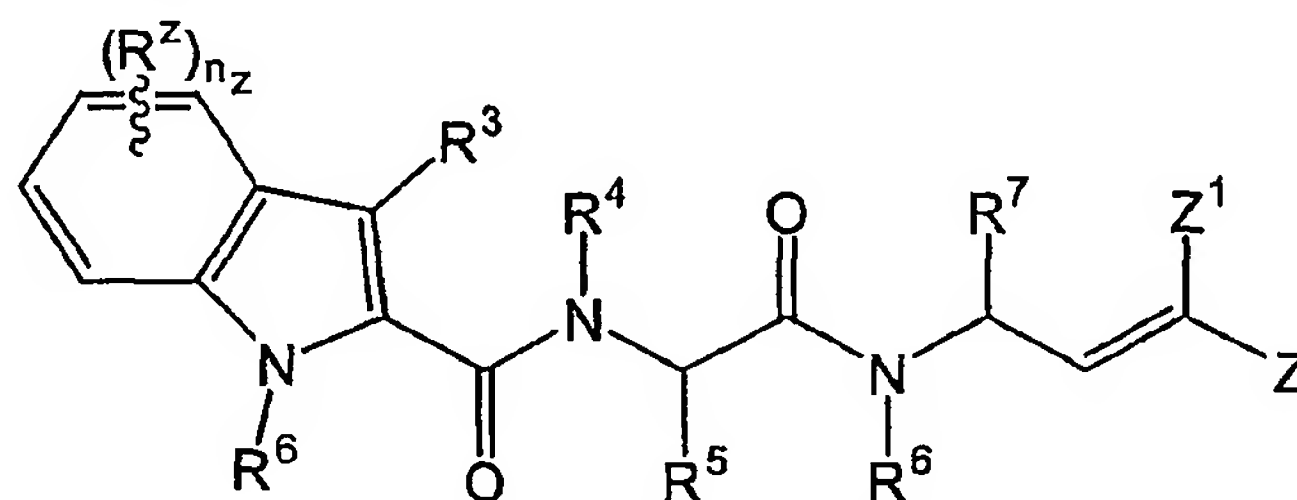
- 59 -



attached form

or a prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate of said compound.

Yet another specific embodiment of this invention comprises the compounds depicted by the formula:



XI

wherein:

each R^Z is independently selected from halo and a C_1 - C_4 alkoxy, C_1 - C_4 alkyl, aryl, heterocycloalkyl or heteroaryl group where the C_1 - C_4 alkoxy or C_1 - C_4 alkyl group is unsubstituted or substituted with one or more substituents independently selected from halo, C_1 - C_4 alkoxy or C_1 - C_4 haloalkoxy and the aryl, heterocycloalkyl or heteroaryl group is unsubstituted or substituted by one or more substituents independently selected from halo, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy and methylenedioxy and n_Z is an integer from 1 to 4; preferably, each R^Z is independently selected from halo, C_1 - C_4 alkoxy, unsubstituted C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, and C_1 - C_4 alkoxyalkyl and n_Z is an integer from 1 to 2; more preferably, each R^Z is independently selected from halo, C_1 - C_4 alkoxy, unsubstituted C_1 - C_4 alkyl and C_1 - C_4 haloalkyl, and n_Z is 1 or 2;

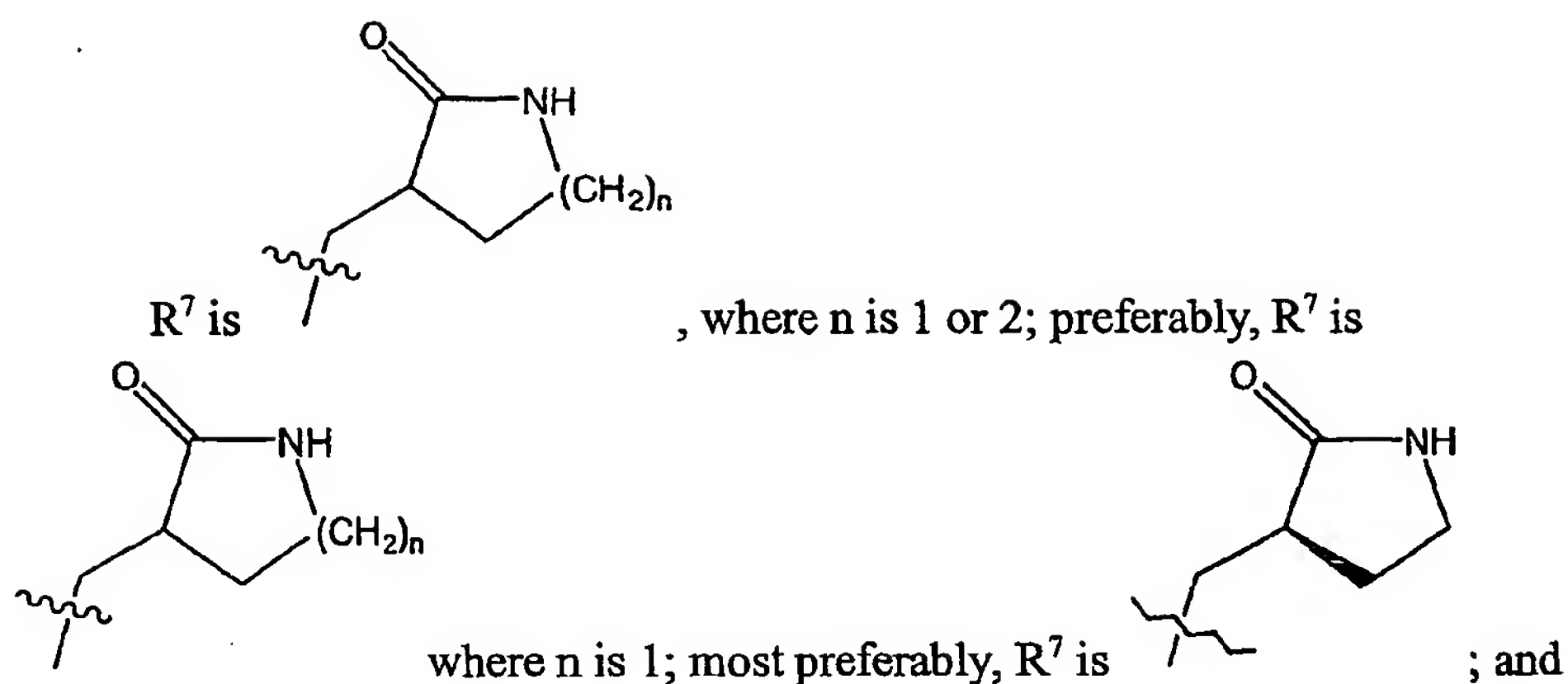
R^3 is H, halo, C_1 - C_4 alkoxy, unsubstituted C_1 - C_4 alkyl, C_1 - C_4 haloalkyl and C_1 - C_4 alkoxyalkyl; preferably, R^3 is H or C_1 - C_4 alkyl; more preferably, R^3 is H;

- 60 -

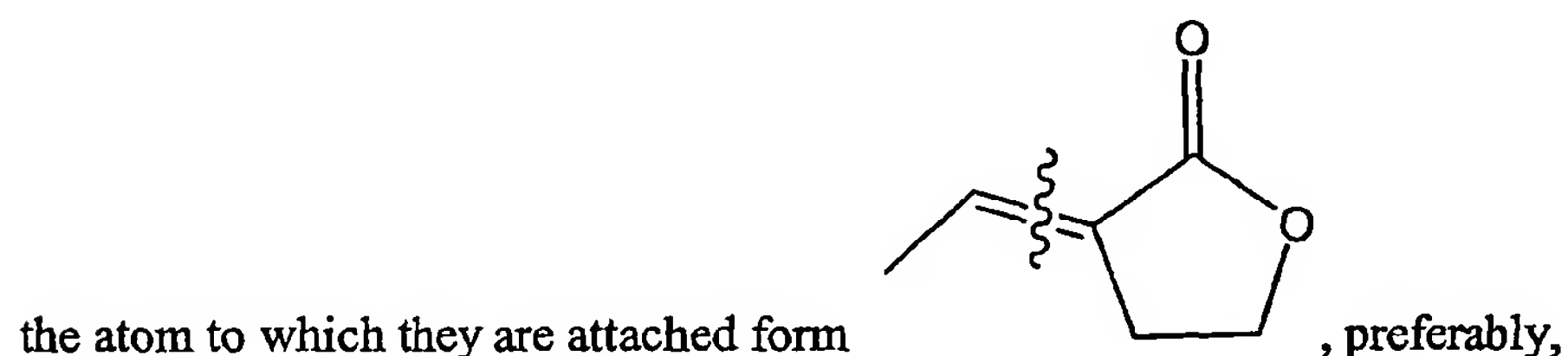
R^4 and each R^6 are independently selected from H, unsubstituted lower alkyl, haloalkyl and lower alkoxyalkyl, preferably, R^4 and each R^6 are independently H or C_1 - C_4 alkyl; more preferably R^4 and R^6 are each H;

R^5 is H, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl or an arylalkyl, heteroarylalkyl, cycloalkylalkyl group or a straight-chain saturated hydrocarbon moiety or an unsaturated hydrocarbon moiety, where the arylalkyl, heteroarylalkyl, cycloalkylalkyl group is unsubstituted or substituted with one or more suitable substituents; preferably, R^5 is H or substituted or unsubstituted methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, -methylcyclohexyl, -methylthienyl or benzyl, where the substituted methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, and -methylcyclohexyl is substituted by one or more substituents independently selected from halo, alkoxy, aryloxy, alkylthio and arylthio; the substituted thienyl is substituted by one or more substituents independently selected from lower alkyl, lower alkoxy, hydroxy, amino, alkylamino, dialkylamino and halo; and the phenyl moiety of the substituted benzyl is substituted by one or more substituents independently selected from lower alkyl, lower alkoxy, alkylenedioxy, hydroxy, amino, alkylamino, dialkylamino and halo; more preferably, R^5 is H, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, -methylcyclohexyl, benzyl or substituted benzyl, wherein the phenyl moiety of the substituted benzyl comprises one or more substituents independently selected from C_1 - C_4 alkyl, C_1 - C_4 alkoxy and halo; even more preferably, R^5 is H, ethyl, 2-propyn-1-yl, methylcyclohexyl or benzyl;

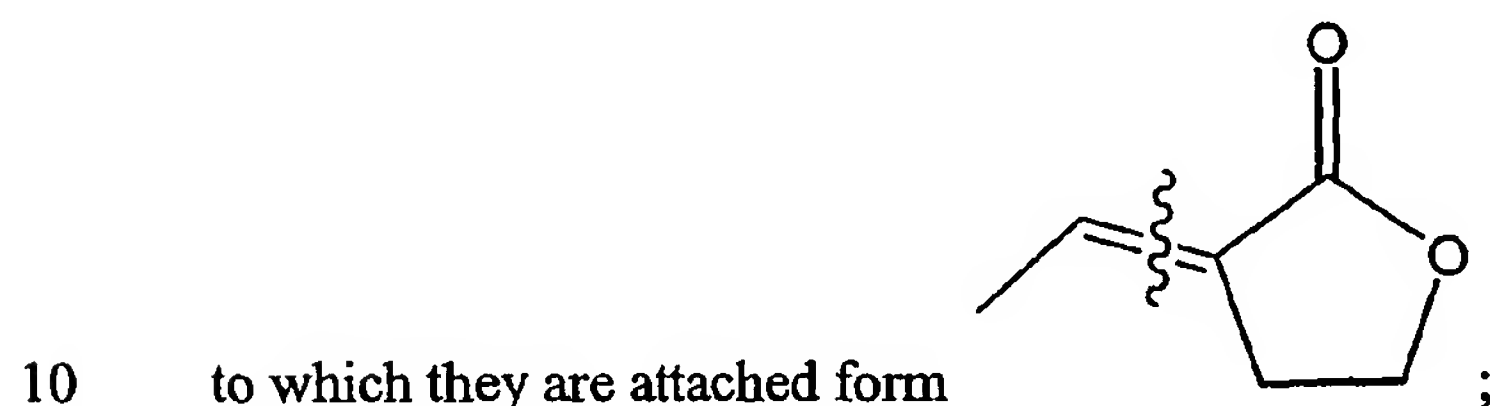
- 61 -



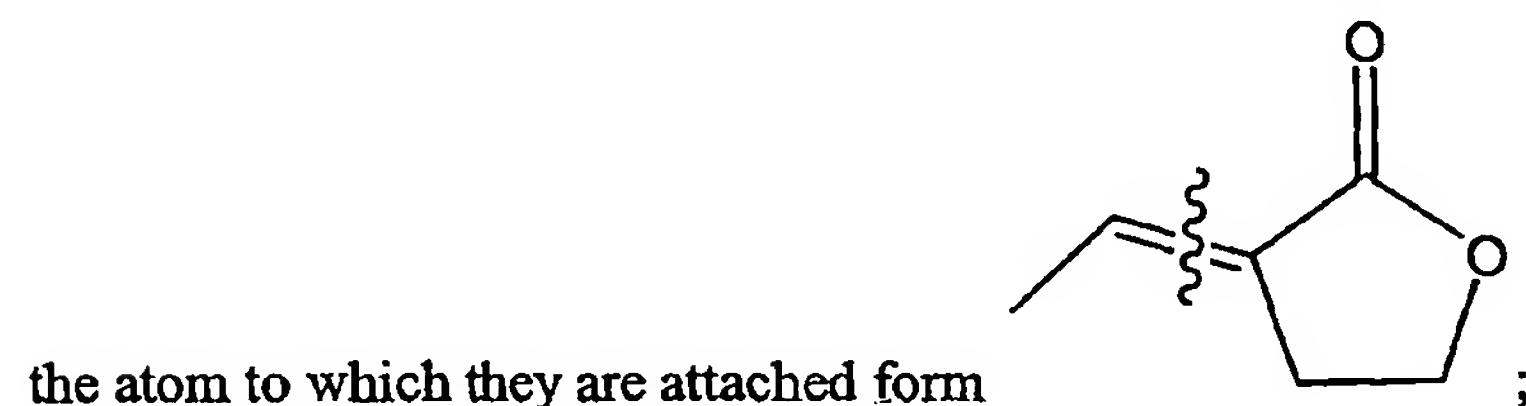
Z^1 is H or C_1 - C_4 alkyl and Z is $-\text{CO}_2$ -alkyl, $-\text{CO}_2$ -cycloalkyl,
 5 $-\text{CO}_2$ -alkylaryl or $-\text{CO}_2$ -alkylheterocycloaryl, or Z^1 and Z taken together with



Z^1 is H and Z is $-\text{CO}_2\text{CH}_2\text{CH}_3$, $-\text{CO}_2(\text{CH}(\text{CH}_3)_2)$, $-\text{CO}_2(\text{C}(\text{CH}_3)_3)$, $-\text{CO}_2\text{CH}_2(\text{C}(\text{CH}_3)_3)$,
 $-\text{CO}_2(\text{cyclo-C}_5\text{H}_9)$ or Z^1 and Z taken together with the atom



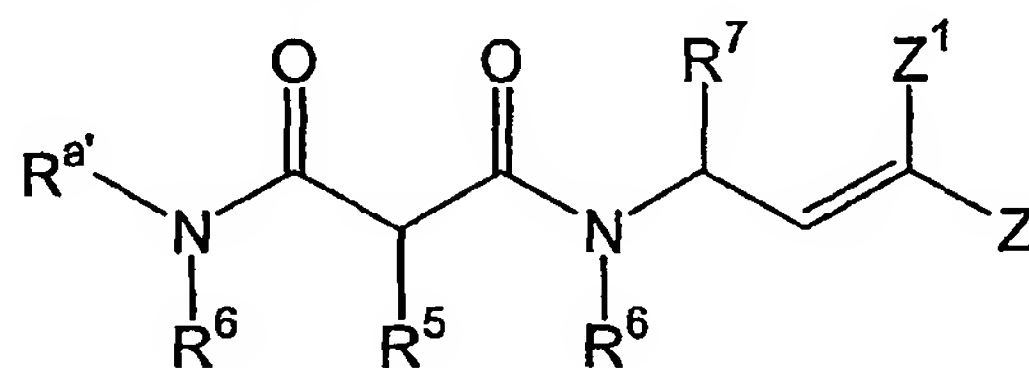
most preferably, Z^1 is H and Z is $-\text{CO}_2\text{CH}_2\text{CH}_3$ or Z^1 and Z taken together with



15 or a prodrug, pharmaceutically acceptable salt, pharmaceutically active
 metabolite, or pharmaceutically acceptable solvate of said compound.

- 62 -

Another preferred embodiment of this invention comprises the compounds of Formula XII, depicted by the formula:



XII

wherein:

$R^{a'}$ is a C_1 - C_4 alkyl, aryl, C_3 - C_7 cycloalkyl, heterocycloalkyl or heteroaryl group, where the C_1 - C_4 alkyl, aryl, C_3 - C_7 cycloalkyl, heterocycloalkyl or heteroaryl group is unsubstituted or substituted with one or more substituents independently selected from alkyl, haloalkyl, alkylenedioxy (as a substituent for aryl or heteroaryl), nitro, amino, hydroxamino, alkylamino, dialkylamino, halo, hydroxyl, alkoxy, haloalkoxy, aryloxy, mercapto, alkylthio or arylthio, aryl or heteroaryl, where the aryl or heteroaryl group is unsubstituted or substituted with one or more substituents independently selected from halo, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy and methylenedioxy; preferably, $R^{a'}$ is a C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, phenyl, naphthyl, C_5 - C_6 cycloalkyl, isoquinoyl, pyridyl or pyrrolyl group, where the phenyl, naphthyl, isoquinoyl, pyridyl or pyrrolyl group is unsubstituted or substituted with one or more substituents independently selected from halo, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy and methylenedioxy; more preferably, $R^{a'}$ is a phenyl group, where the phenyl group is unsubstituted or substituted with one or more substituents independently selected from halo, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl or C_1 - C_4 alkoxy;

each R^6 is independently H or C_1 - C_4 alkyl; preferably, each R^6 is H;

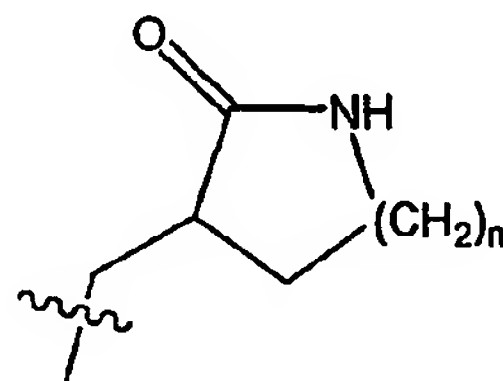
R^5 is H, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl or an arylalkyl, heteroarylalkyl, cycloalkylalkyl group or a straight-chain saturated hydrocarbon moiety or an unsaturated hydrocarbon moiety, where the arylalkyl, heteroarylalkyl, cycloalkylalkyl group is unsubstituted or substituted with one or more suitable substituents; preferably, R^5 is H or substituted or unsubstituted methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl,

- 63 -

3-methyl-3-buten-1-yl, -methylcyclohexyl, -methylthienyl or benzyl, where the substituted methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, and -methylcyclohexyl is substituted by one or more substituents independently selected from halo, alkoxy, aryloxy, alkylthio and arylthio; the substituted thienyl is substituted by one or more substituents independently selected from lower alkyl, lower alkoxy, hydroxy, amino, alkylamino, dialkylamino and halo; and the phenyl moiety of the substituted benzyl is substituted by one or more substituents independently selected from lower alkyl, lower alkoxy, alkylendioxy, hydroxy, amino, alkylamino, dialkylamino and halo; more preferably, R⁵ is H, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, -methylcyclohexyl, benzyl or substituted benzyl, wherein the phenyl moiety of the substituted benzyl comprises one or more substituents independently selected from C₁-C₄ alkyl, C₁-C₄ alkoxy and halo; even more preferably, R⁵ is H, ethyl, 2-propyn-1-yl, methylcyclohexyl or benzyl;

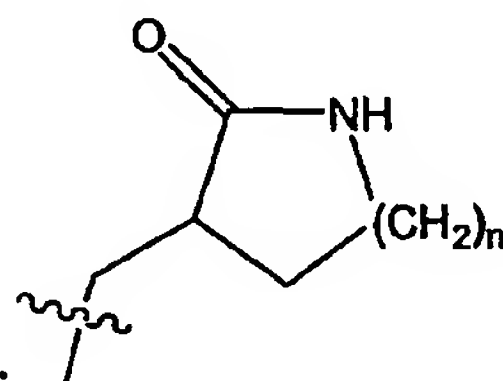
R⁷ is selected from -CH₂CH₂C(O)NH₂; -CH₂CH₂C(O)NH-alkyl;

-CH₂NHC(O)CH₃; and



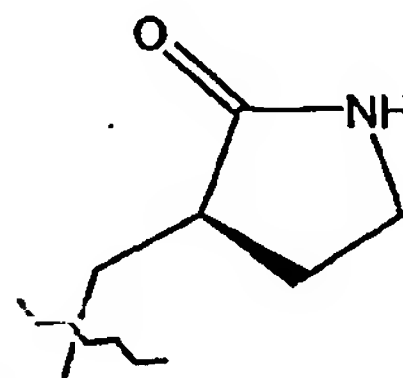
, where n is 1 or 2;

preferably, R⁷ is -CH₂CH₂C(O)NH₂ or



, where n is 1;

most preferably, R⁷ is -CH₂CH₂C(O)NH₂ or

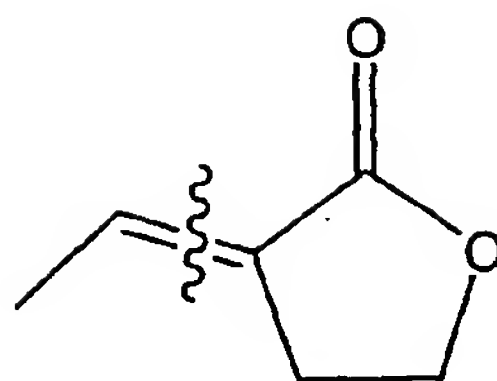


; and

Z¹ is H or C₁-C₄ alkyl and Z is -CO₂-alkyl, -CO₂-cycloalkyl, -CO₂-alkylaryl or -CO₂-alkylheterocycloaryl, or Z¹ and Z taken together with the

- 64 -

atom to which they are attached form

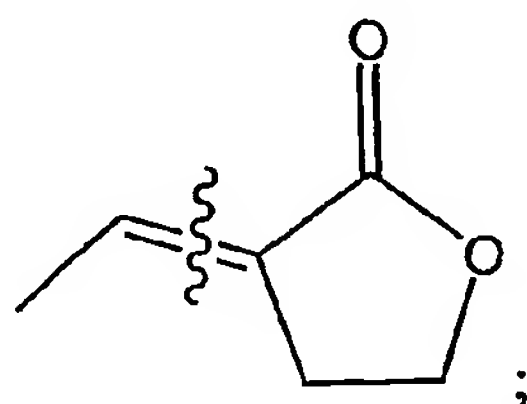


, preferably, Z^1 is H

and Z is $-\text{CO}_2\text{CH}_2\text{CH}_3$, $-\text{CO}_2(\text{CH}(\text{CH}_3)_2)$, $-\text{CO}_2(\text{C}(\text{CH}_3)_3)$, $-\text{CO}_2\text{CH}_2(\text{C}(\text{CH}_3)_3)$, $-\text{CO}_2(\text{cyclo-C}_5\text{H}_9)$ or Z^1 and Z taken together with the atom to which they are

5

attached form

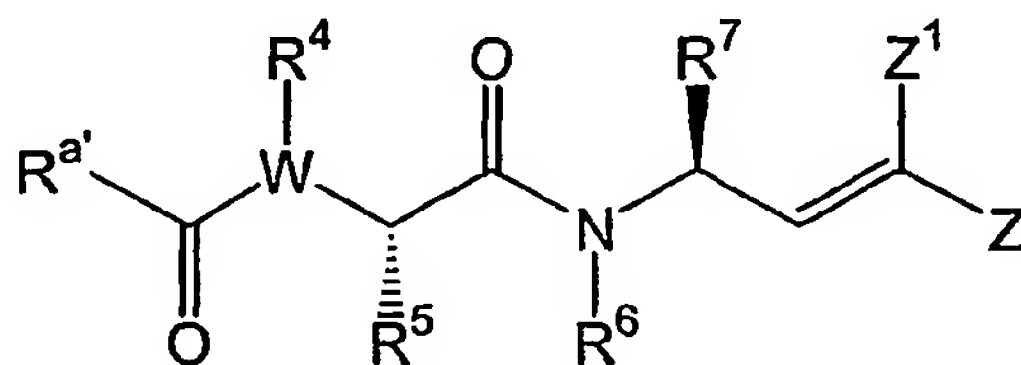


most preferably, Z^1 is H and Z is $-\text{CO}_2\text{CH}_2\text{CH}_3$ or Z^1 and Z taken together with

10

or a prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate of said compound.

Preferred embodiments of this invention comprise the compounds depicted by the formula:



15

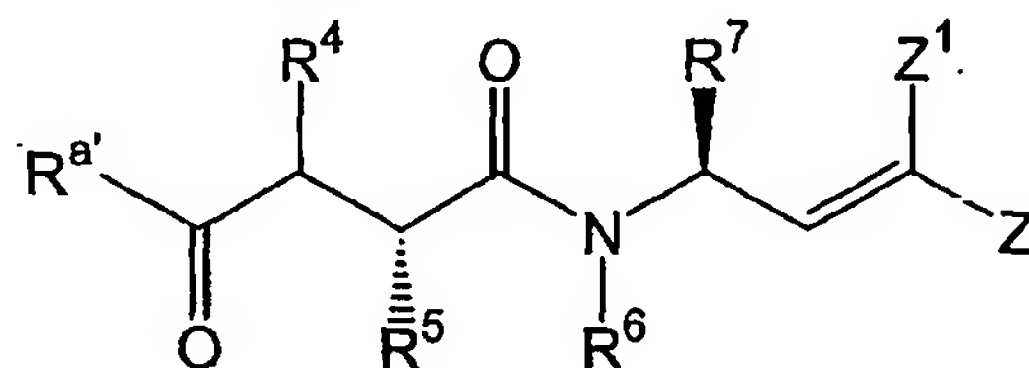
VI-a

20

wherein R^a is an alkyl, cycloalkyl, aryl or heteroaryl group, where said alkyl, cycloalkyl, aryl, and heteroaryl group is unsubstituted or substituted with one or more suitable substituents, and each W, R^4 , R^5 , R^6 , R^7 , Z and Z^1 are as defined in VI above, provided that R^a is not amino-substituted alkyl.

- 65 -

Particularly preferred embodiments of the compounds of Formula VI-a comprise the compounds depicted by the formula:



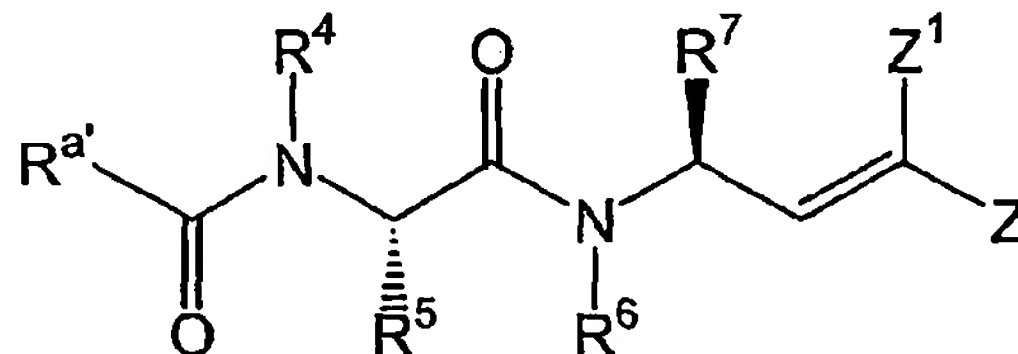
VII-a

5

wherein R^{a'} is an alkyl, cycloalkyl, aryl or heteroaryl group, where said alkyl, cycloalkyl, aryl, and heteroaryl group is unsubstituted or substituted with one or more suitable substituents, and each R⁴, R⁵, R⁶, R⁷, Z and Z¹ are as defined above, provided that R^{a'} is not amino-substituted alkyl.

10

Other preferred embodiments of the compounds of Formula VI-a comprise the compounds depicted by the formula:



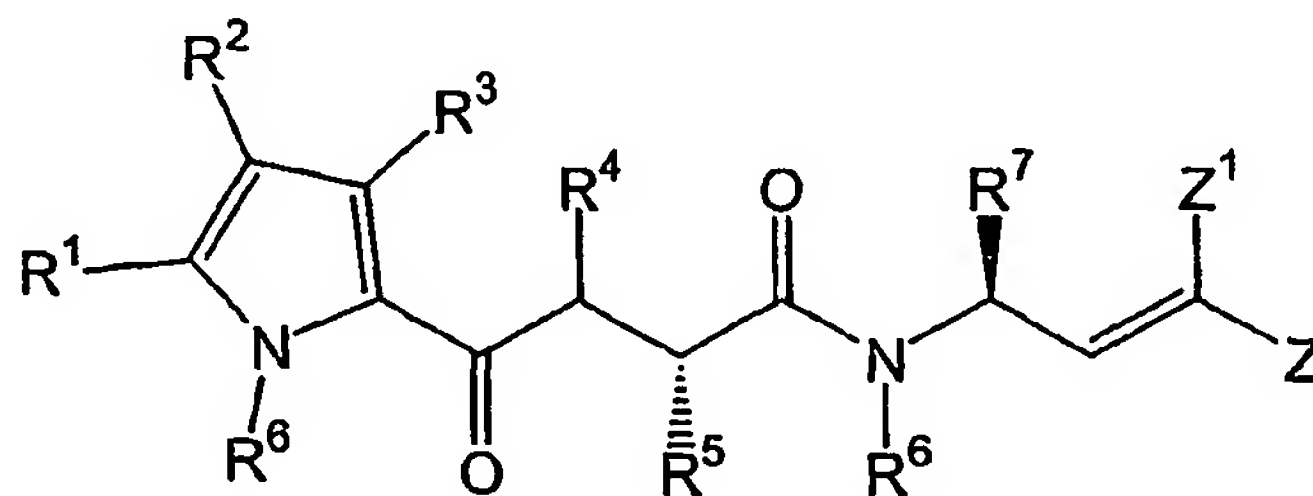
VIII-a

15

wherein R^{a'} is an alkyl, cycloalkyl, aryl or heteroaryl group, where said alkyl, cycloalkyl, aryl, and heteroaryl group is unsubstituted or substituted with one or more suitable substituents, and each R⁴, R⁵, R⁶, R⁷, Z and Z¹ are as defined above, provided that R^{a'} is not amino-substituted alkyl.

20

More preferably, the compounds of this invention have the formula:



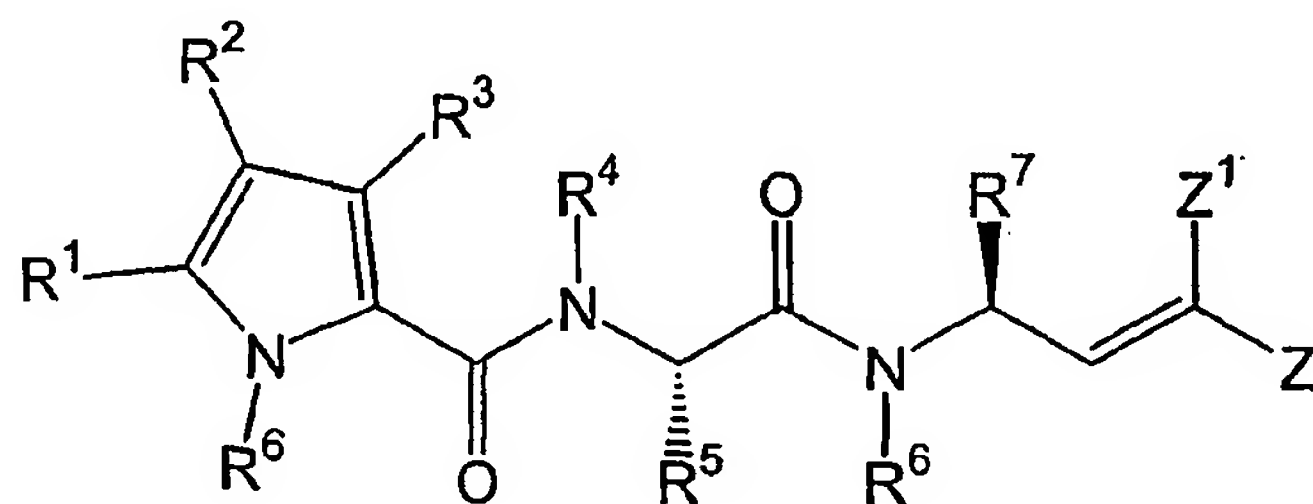
IX-a

25

- 66 -

wherein R^1 is an alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group, where the alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl group is unsubstituted or substituted with one or more suitable substituents, and each R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , Z and Z^1 are as defined above for IX.

5 In another preferred embodiment, the compounds of this invention have the formula:

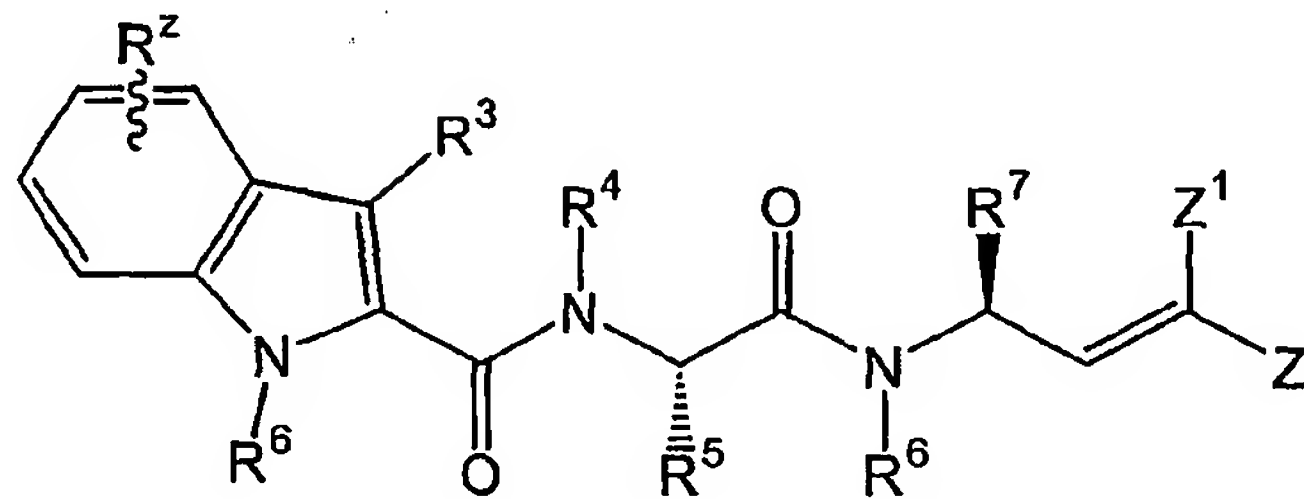


X-a

10

wherein each R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , Z and Z^1 are as defined above.

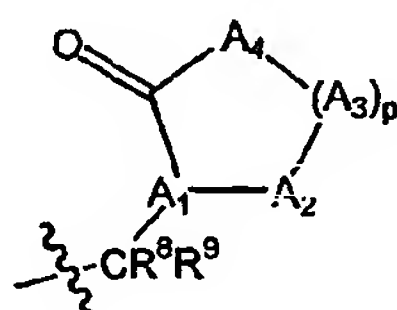
Yet another preferred embodiment of this invention comprises the compounds depicted by the formula:



XI-a

15

wherein each R^2 , R^3 , R^4 , R^5 , R^6 , Z and Z^1 are as defined above and R^7 is a moiety having the formula:

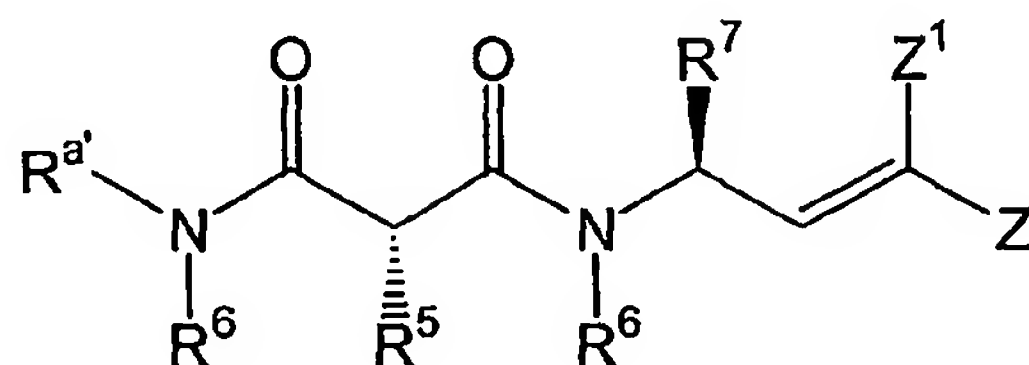


20

wherein each R^8 , R^9 , A_1 , A_2 , A_3 , A_4 and p are as defined above.

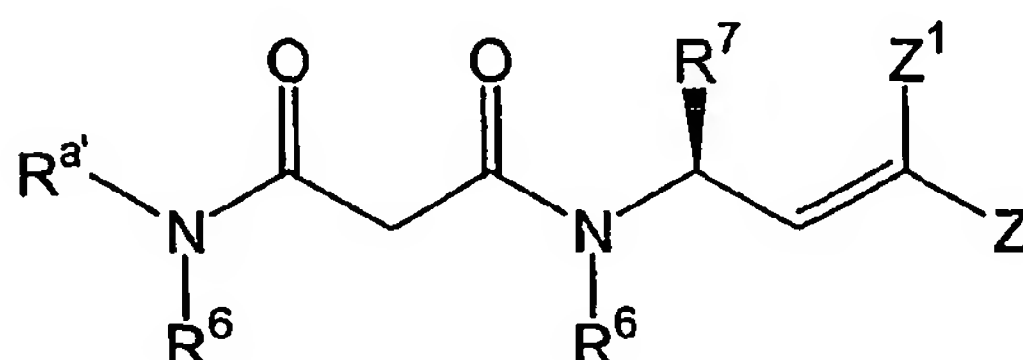
- 67 -

Another particularly preferred embodiment of this invention comprises the compounds depicted by the formula:



XII-a

wherein each R^a , R^5 , R^6 , R^7 , Z and Z^1 are as defined above. More preferably, R^5 is H and the invention comprises the compounds depicted by the formula:

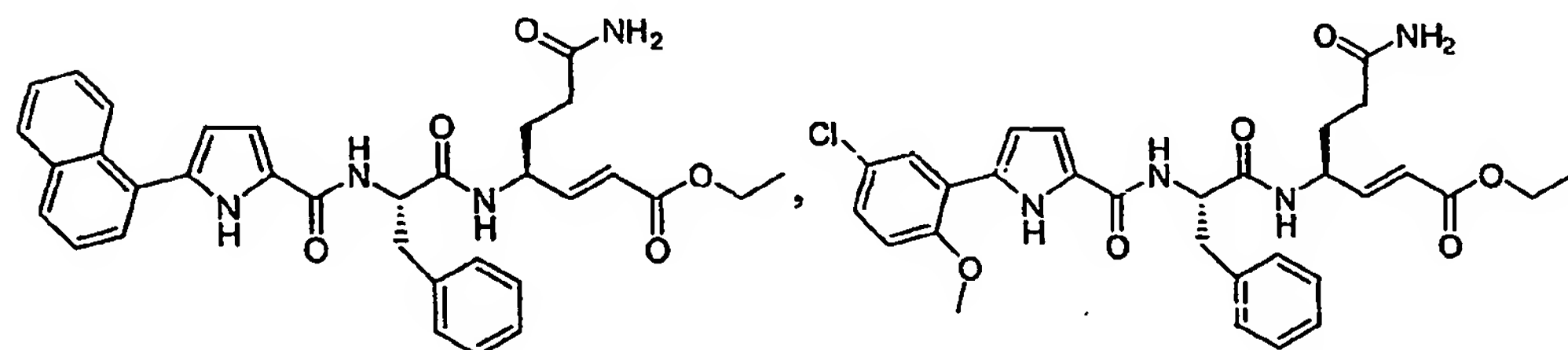
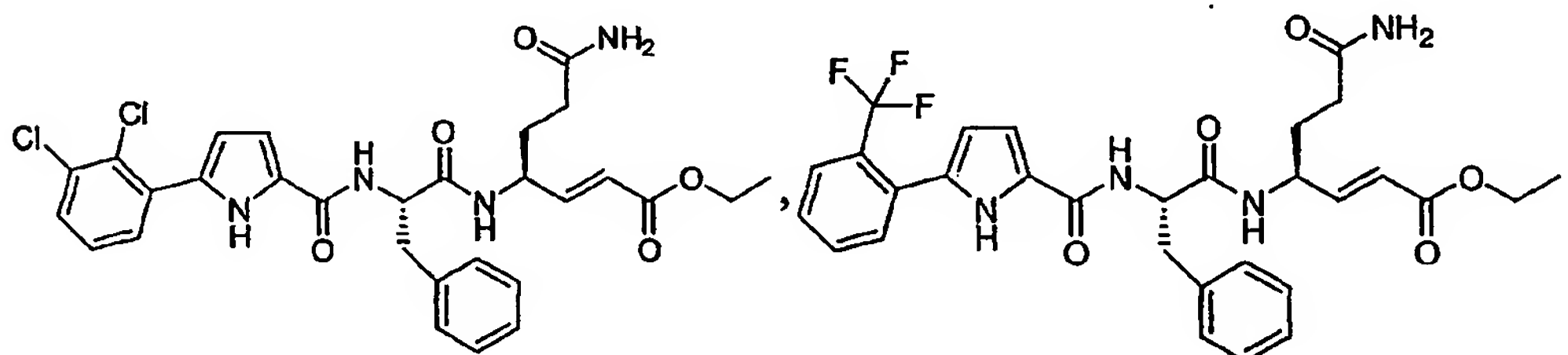


XII-b

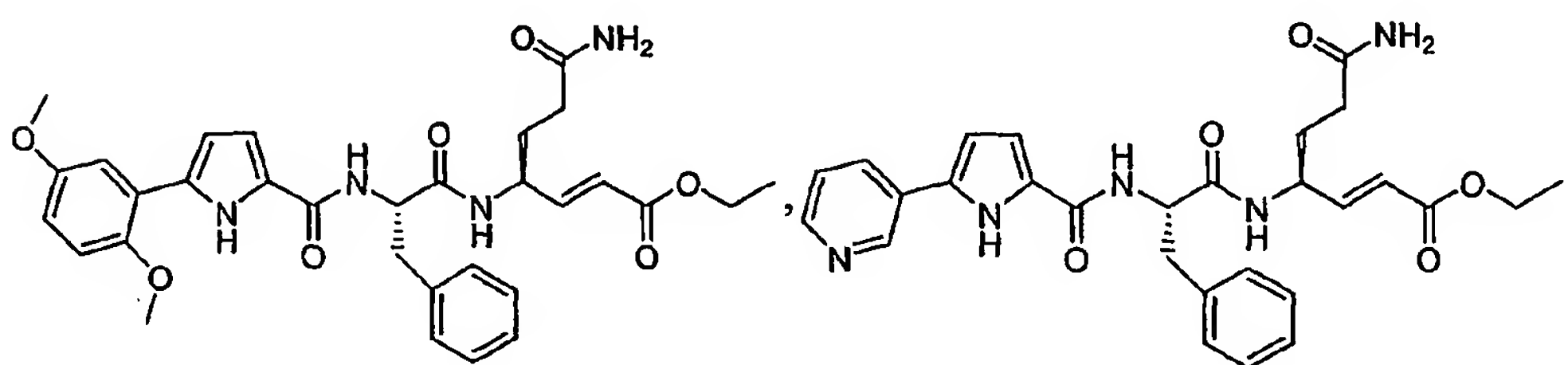
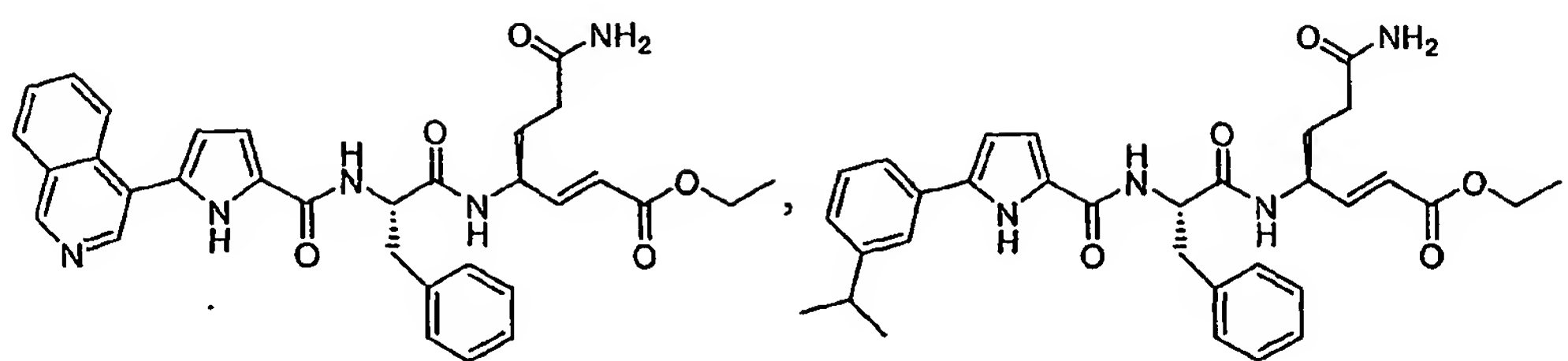
wherein each R^a , R^6 , R^7 , Z and Z^1 are as defined above.

In the compounds of Formulas VI-a to XII-b, R^6 is preferably H. In the compounds of Formulas VI-a to XI-a, each R^4 and R^6 is preferably H.

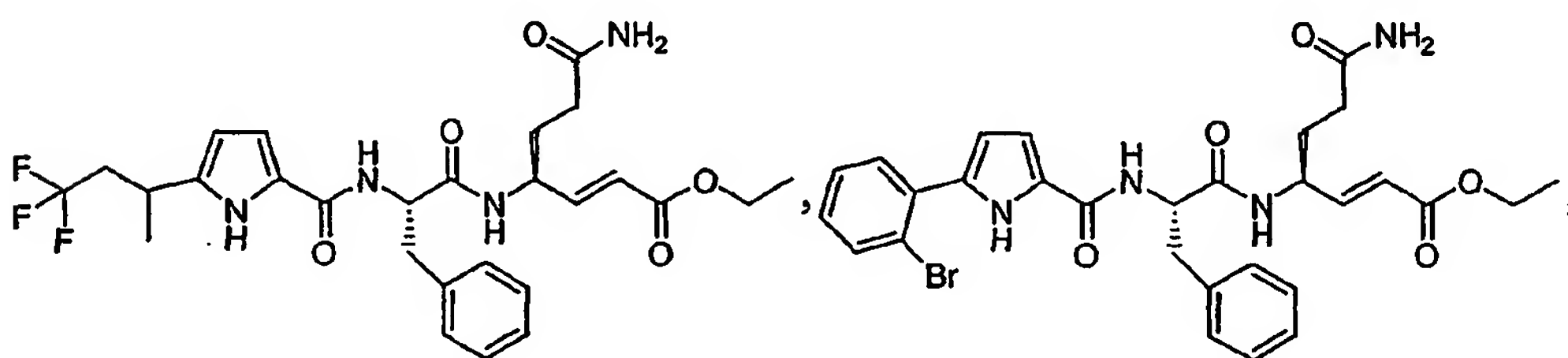
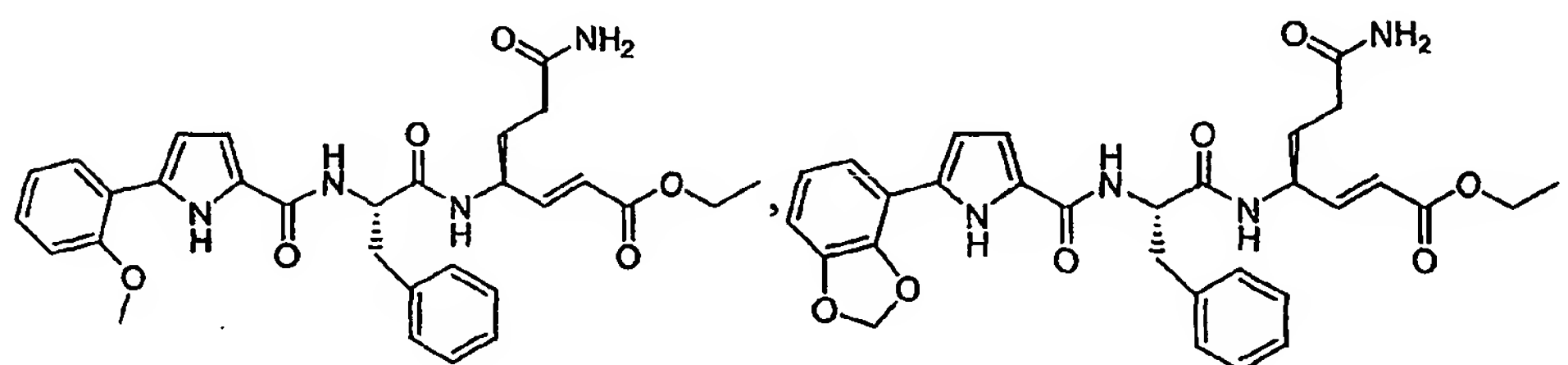
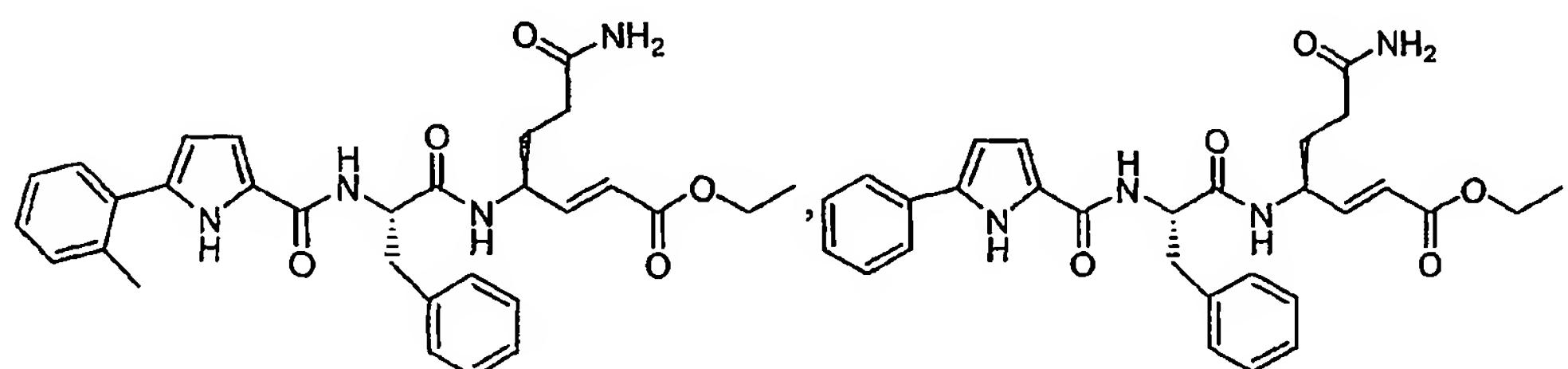
Preferred specific compounds include those of any of the Examples below, especially:



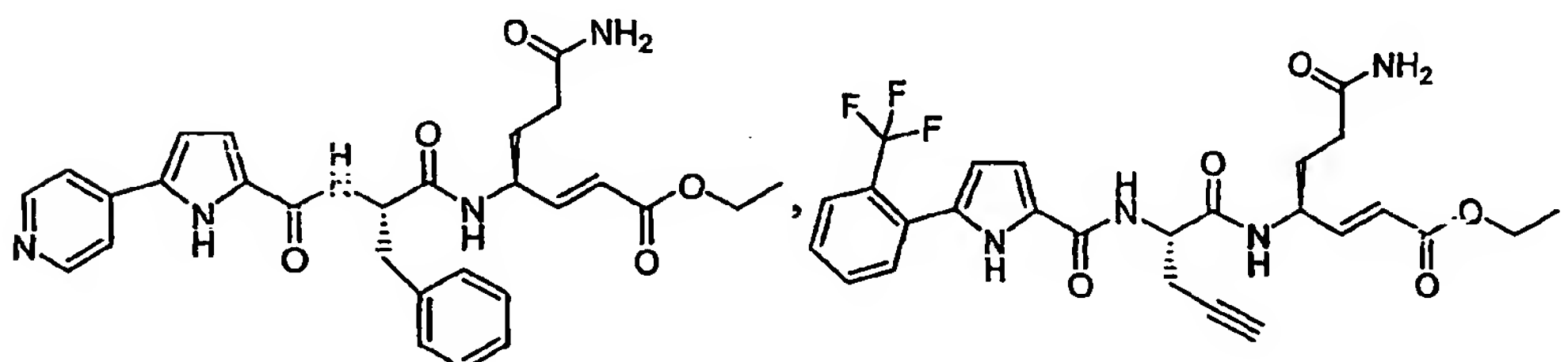
- 68 -



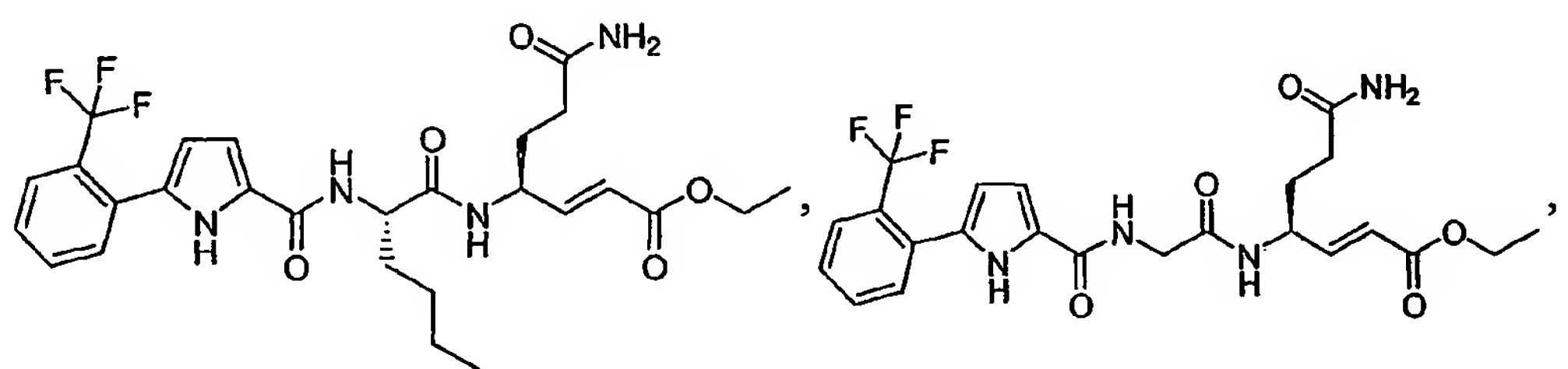
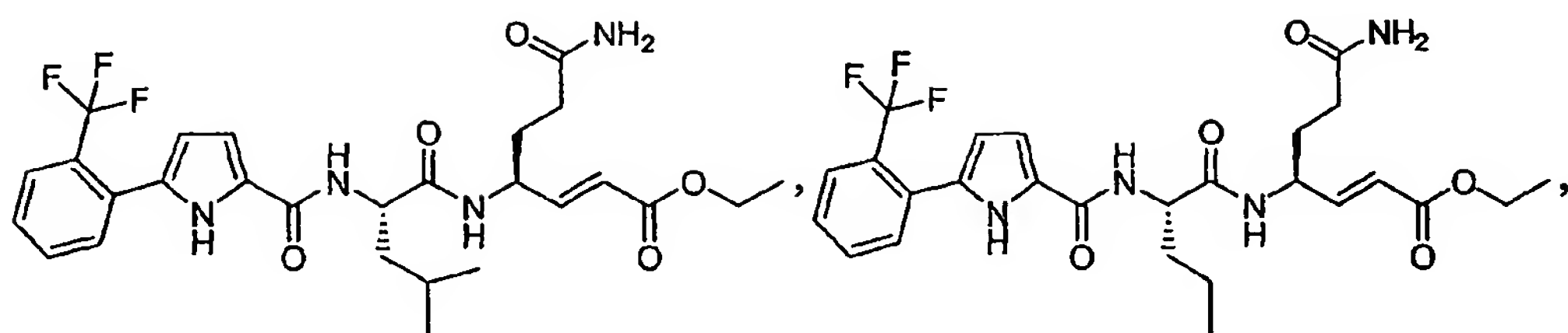
5



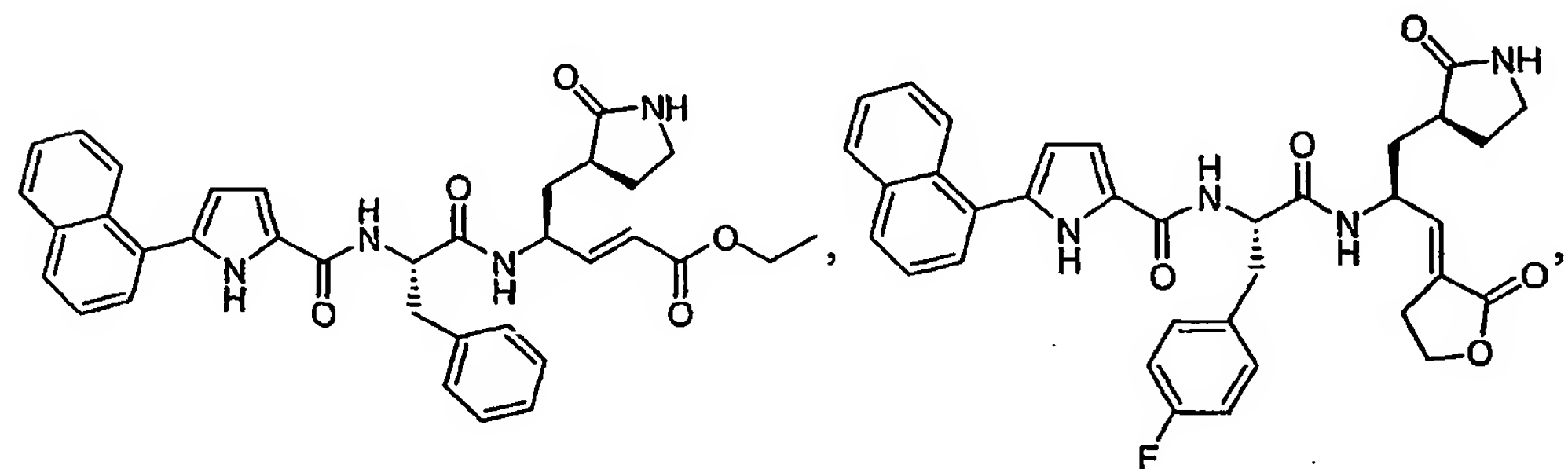
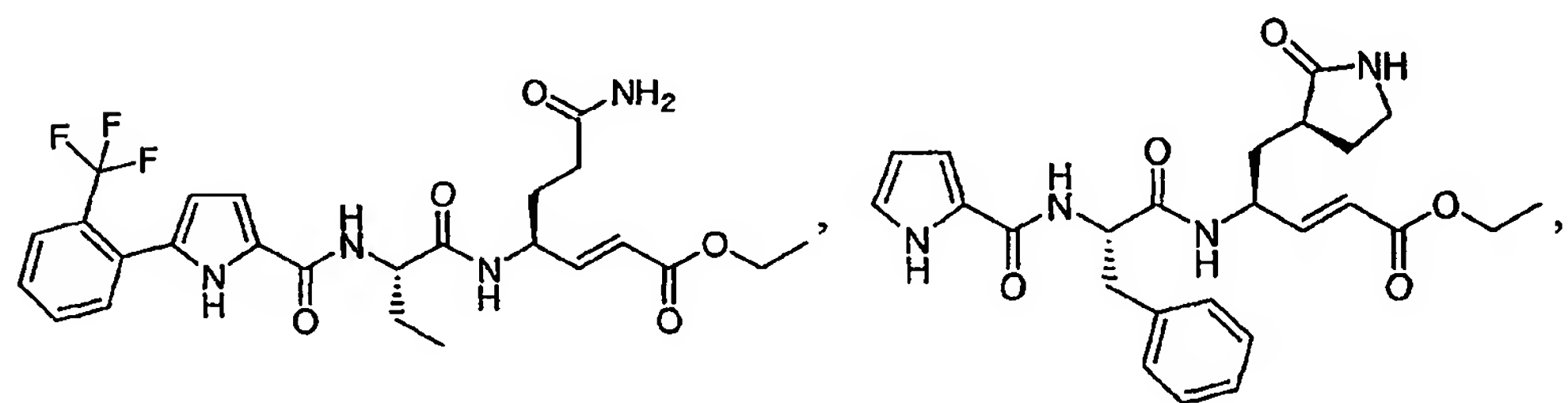
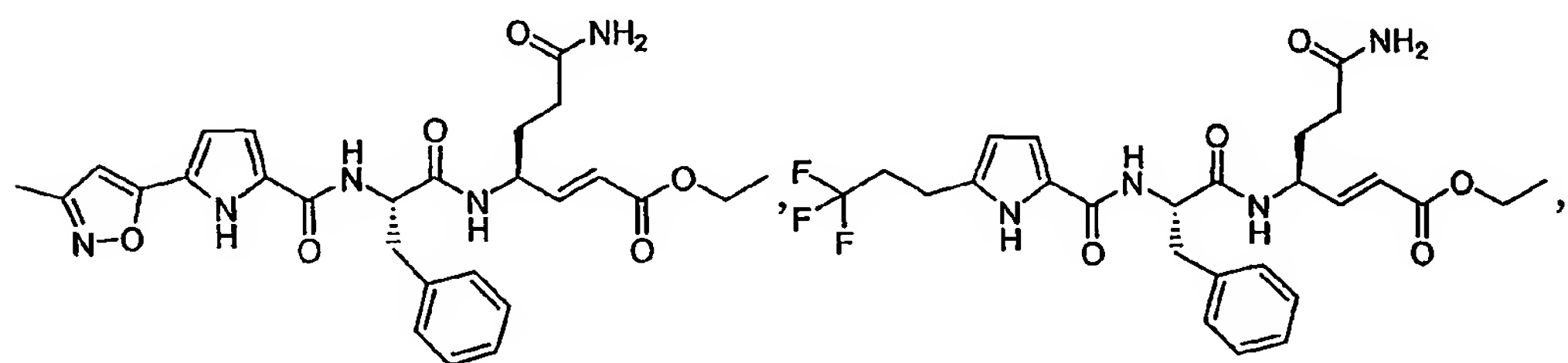
10



- 69 -

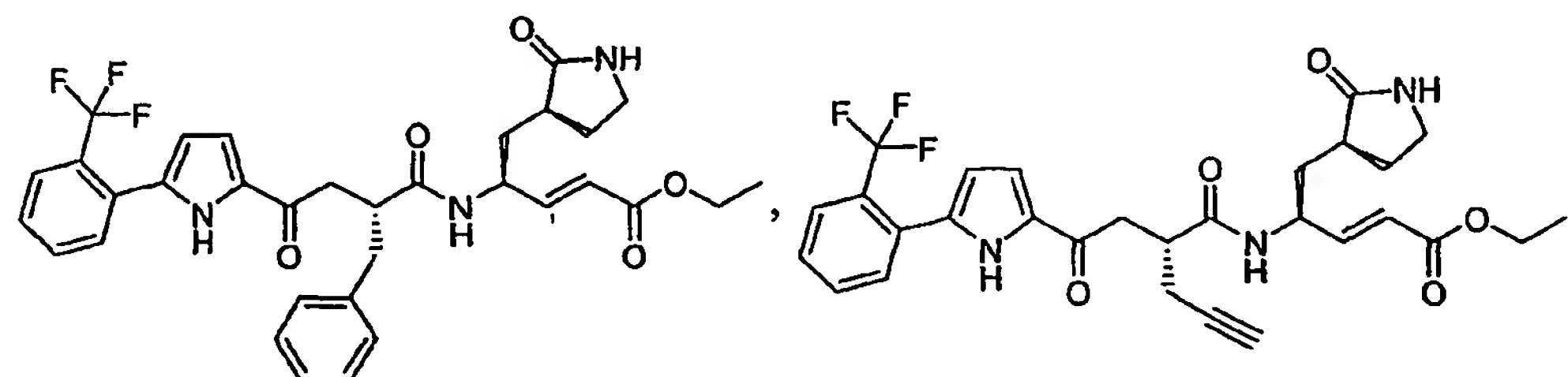
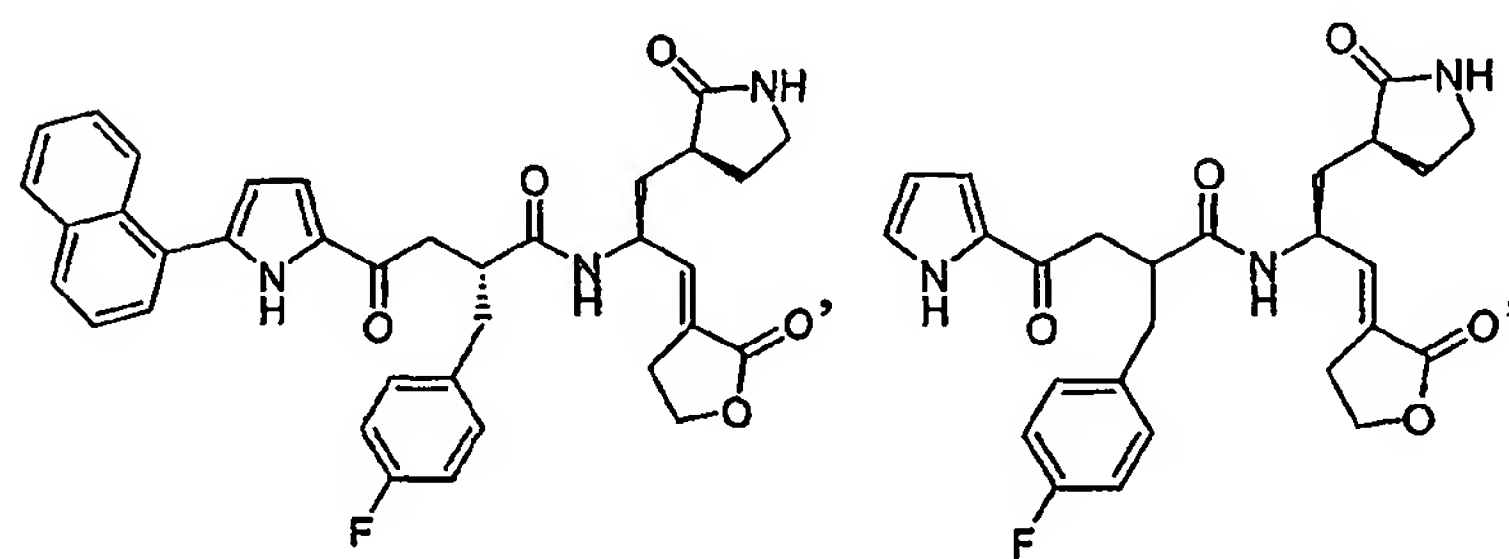
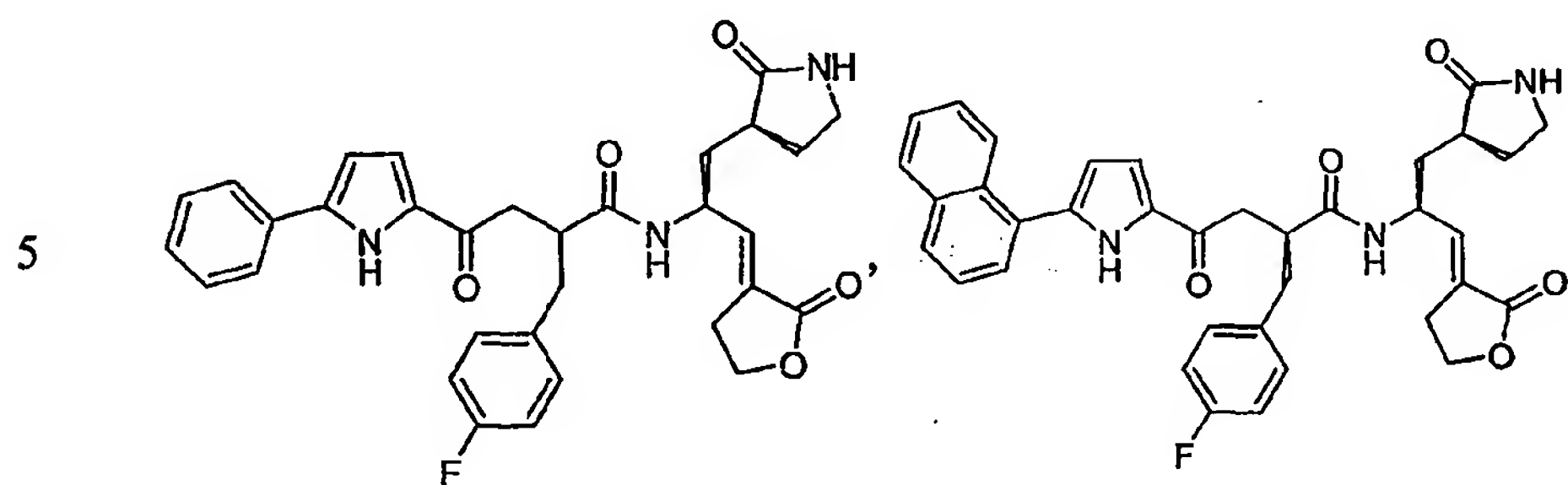
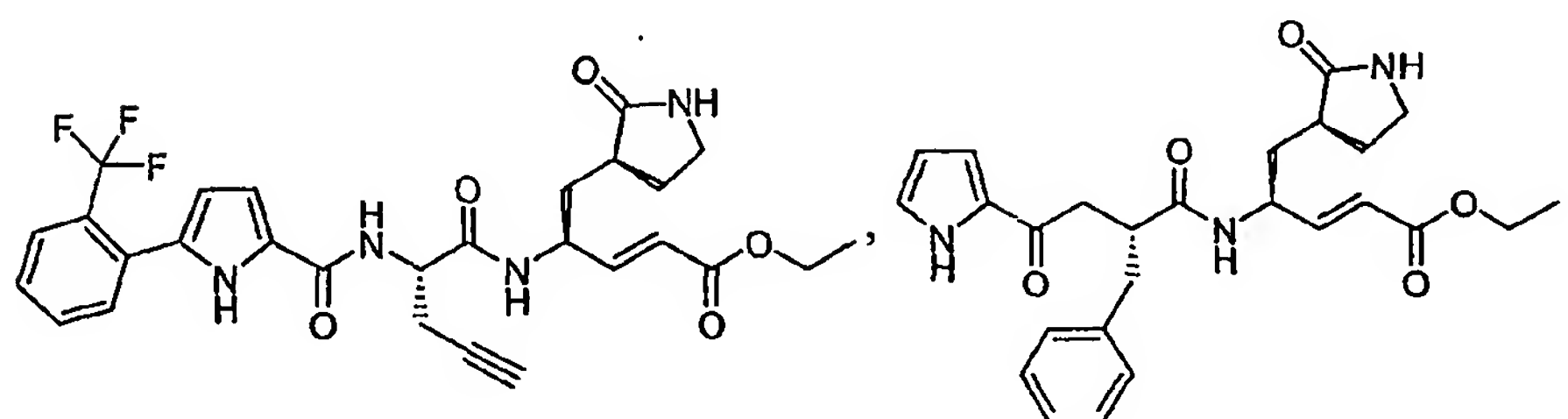
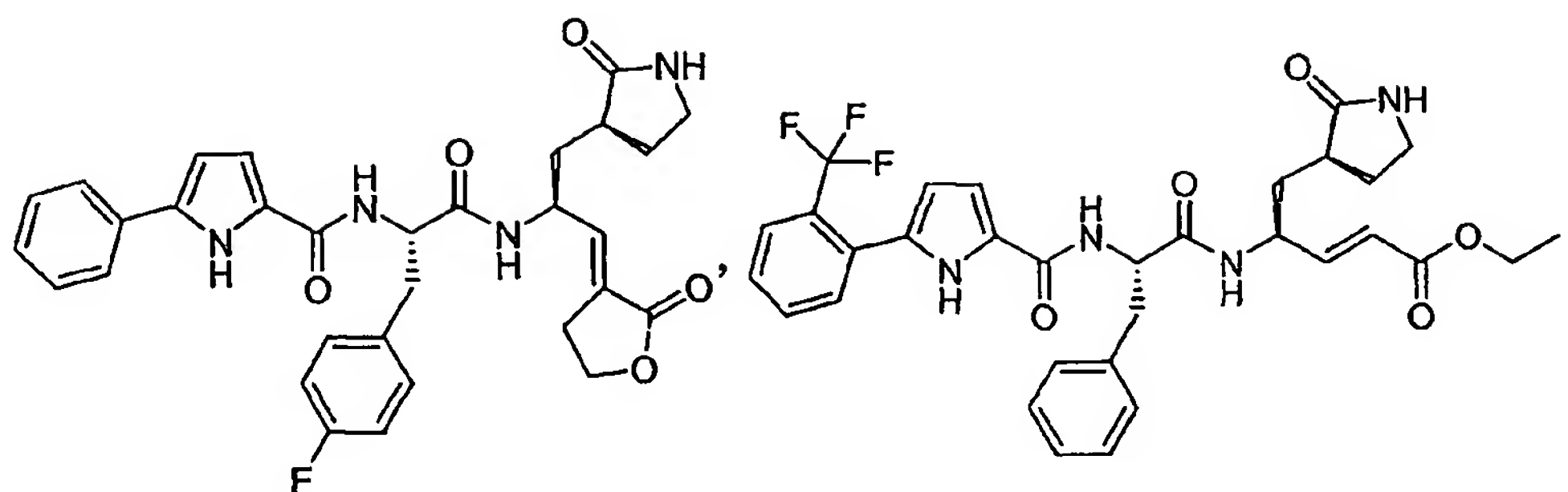


5

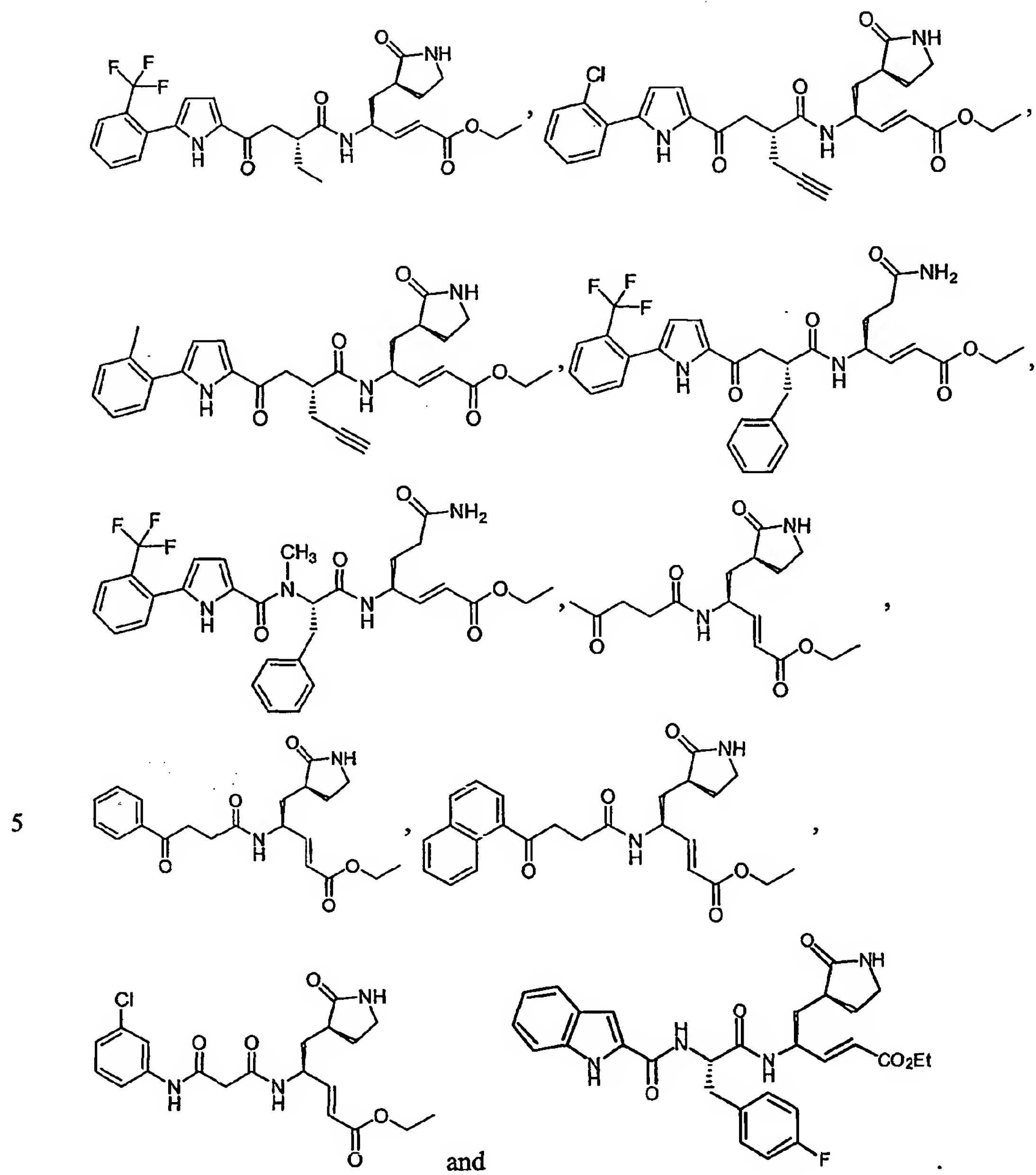


10

- 70 -



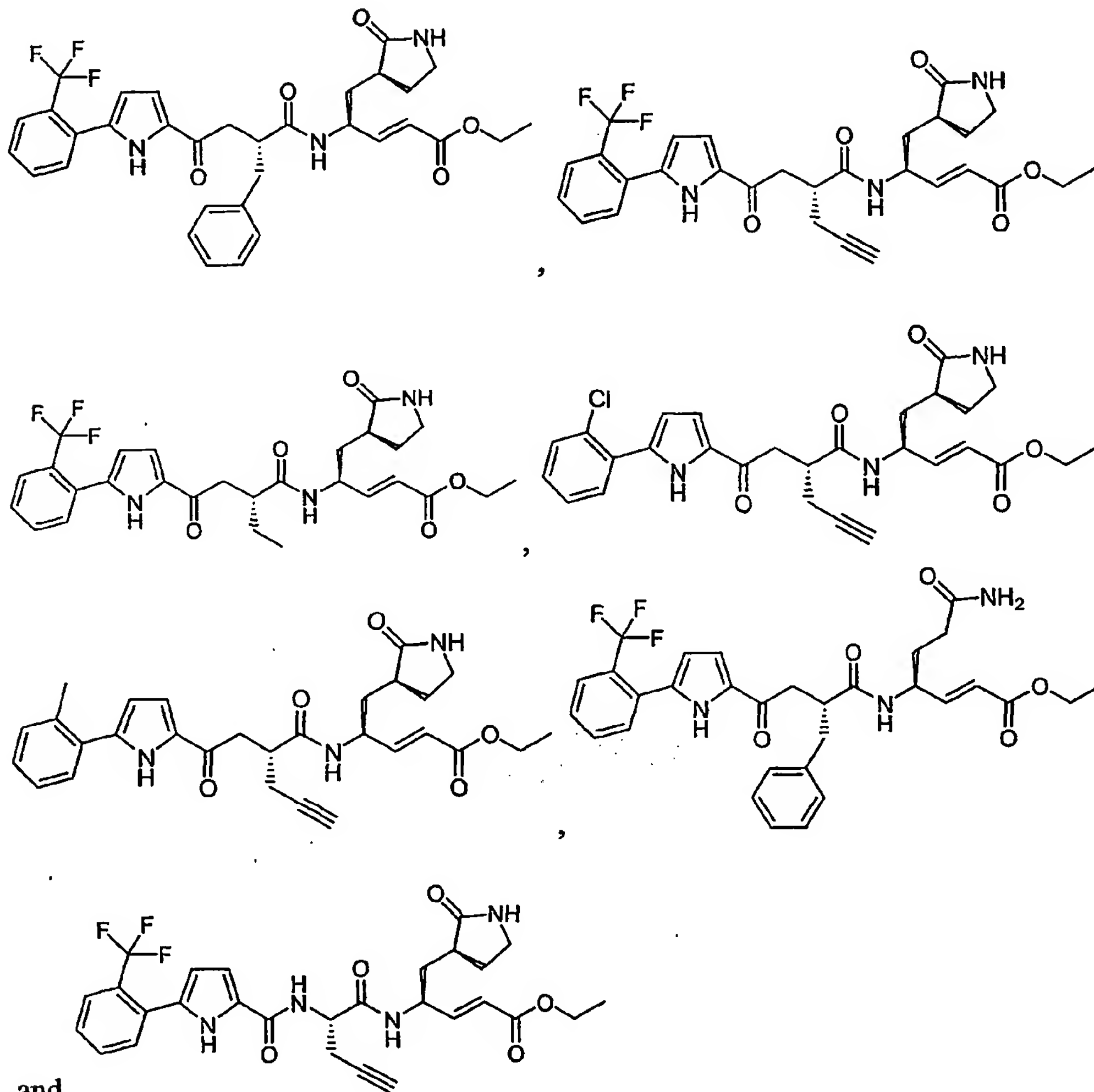
- 71 -



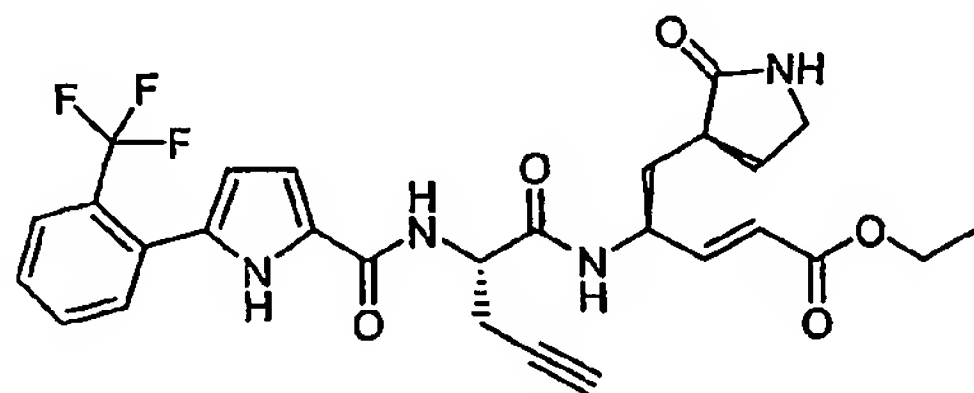
and

- 72 -

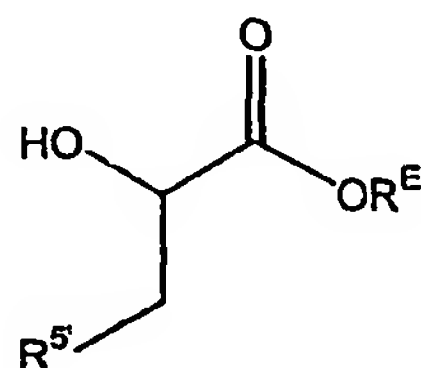
Preferred specific embodiments of the compounds of this invention include any one of the following:



and



The invention is also directed to intermediate compounds of Formula XIII which are useful in the synthesis of certain compounds of Formulas I-XII:

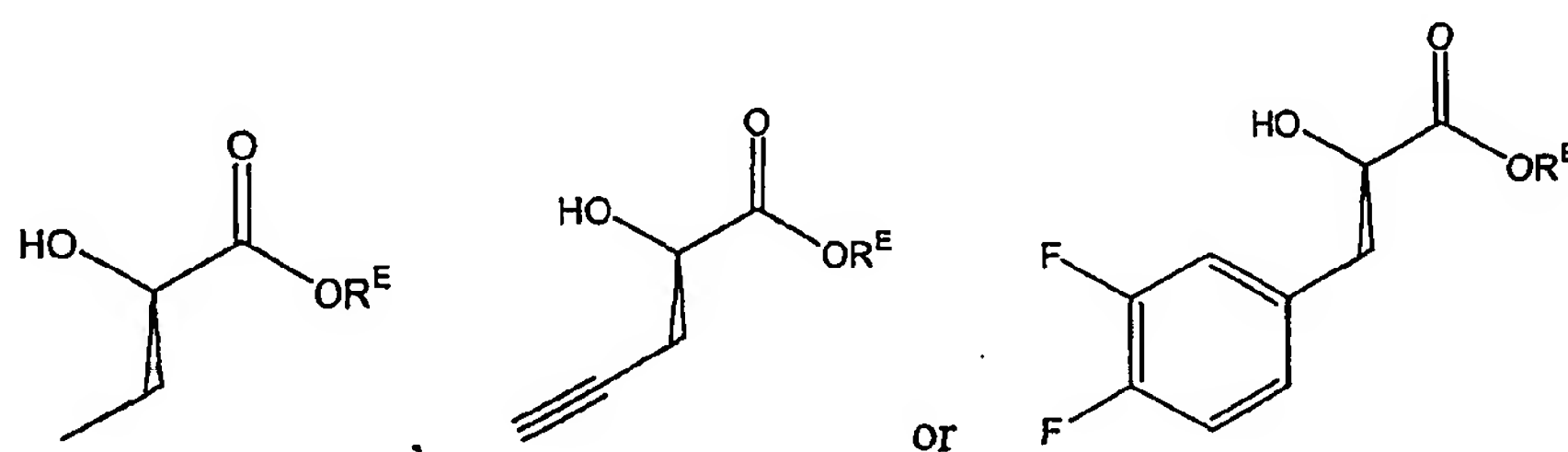


XIII

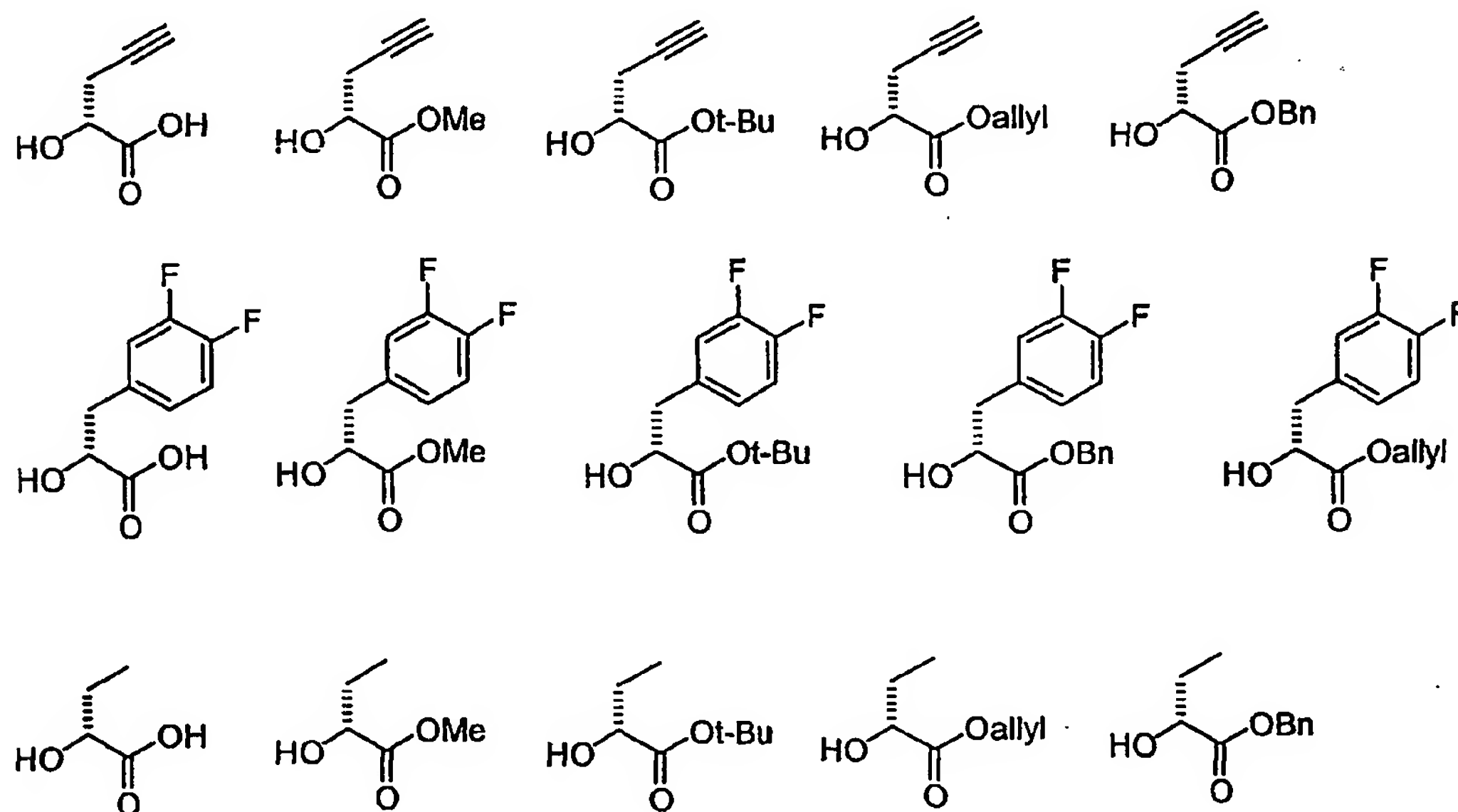
- 73 -

wherein $R^{5'}$ is a lower alkyl or aryl group, where the lower alkyl or aryl group is unsubstituted or substituted with one or more suitable substituents, (where $-CH_2-R^{5'}$ represents R^5 as defined above) and R^E is H or an alkyl or aryl group, where the alkyl or aryl group is unsubstituted or substituted with one or more suitable substituents.

- 5 The invention is also directed to pharmaceutically acceptable salts of the compounds of Formulas XIII. Preferred examples of the compounds of Formula XIII, include the following:



- 10 and pharmaceutically acceptable salts thereof. Exemplary preferred R^E groups include, but are not limited to, H, methyl, *tert*-butyl, allyl, and benzyl, as illustrated in the following:



15

The antipicornaviral compounds of this invention include prodrugs, the pharmaceutically active metabolites, and the pharmaceutically acceptable salts and solvates thereof. In preferred embodiments, the compounds of Formulas I to XII,

- 74 -

prodrugs, pharmaceutically acceptable salts, and pharmaceutically active metabolites and solvates thereof have an antipicornaviral activity, more preferably antirhinoviral activity, corresponding to an EC_{50} less than or equal to 100 μ M in the H1-HeLa cell culture assay.

5 A "prodrug" is intended to mean a compound that is converted under physiological conditions or by solvolysis or metabolically to a specified compound that is pharmaceutically active. A prodrug may be a derivative of one of the compounds of this invention that contains a moiety, such as for example $-CO_2R$, $-PO(OR)_2$ or $-C=NR$, that may be cleaved under physiological conditions or by solvolysis. Any suitable R
10 substituent may be used that provides a pharmaceutically acceptable solvolysis or cleavage product. A prodrug containing such a moiety may be prepared according to conventional procedures by treatment of a compound of this invention containing, for example, an amido, carboxylic acid, or hydroxyl moiety with a suitable reagent. A
15 "pharmaceutically active metabolite" is intended to mean a pharmacologically active compound produced through metabolism in the body of a specified compound. Prodrugs and active metabolites of compounds of this invention of the above-described Formulas may be determined using techniques known in the art, for example, through metabolic studies. See, e.g., "Design of Prodrugs," (Bundgaard, ed.), 1985, Elsevier
20 Publishers B.V., Amsterdam, The Netherlands. A "pharmaceutically acceptable salt" is intended to mean a salt that retains the biological effectiveness of the free acids and bases of a specified compound and that is not biologically or otherwise undesirable. Examples of pharmaceutically acceptable salts include sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrogenphosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, propionates,
25 decanoates, caprylates, acrylates, formates, isobutyrate, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyne-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, sulfonates, xylenesulfonates, phenylacetates, phenylpropionates, phenylbutyrates, citrates, lactates,
30 γ -hydroxybutyrates, glycollates, tartrates, methane-sulfonates (mesylates), propanesulfonates, naphthalene-1-sulfonates, naphthalene-2-sulfonates, and

- 75 -

mandelates. A "solvate" is intended to mean a pharmaceutically acceptable solvate form of a specified compound that retains the biological effectiveness of such compound. Examples of solvates include compounds of the invention in combination with water, isopropanol, ethanol, methanol, DMSO, ethyl acetate, acetic acid, or
5 ethanolamine. In the case of compounds, salts, or solvates that are solids, it is understood by those skilled in the art that the inventive compounds, salts, and solvates may exist in different crystal forms, all of which are intended to be within the scope of the present invention and specified formulas.

The present invention is also directed to a method of inhibiting picornaviral 3C
10 protease activity, comprising contacting the protease with an effective amount of a compound of Formulas I to XII, or a pharmaceutically acceptable salt, prodrug, pharmaceutically active metabolite, or solvate thereof. For example, picornaviral 3C protease activity may be inhibited in mammalian tissue by administering a compound of Formulas I to XII or a pharmaceutically acceptable salt, prodrug, pharmaceutically
15 active metabolite, or solvate thereof. More preferably, the present method is directed at inhibiting rhinoviral protease activity. "Treating" or "treatment" is intended to mean at least the mitigation of a disease condition in a mammal, such as a human, that is alleviated by the inhibition of the activity of one or more picornaviral 3C proteases, including, but not limited to human rhinoviruses, human poliovirus, human
20 coxsackieviruses, encephalomyocarditis viruses, meningitis virus, and hepatitis A virus. The methods of treatment for mitigation of a disease condition include the use of the compounds in this invention in any conventionally acceptable manner, for example, as a prophylactic. The activity of the inventive compounds as inhibitors of picornaviral 3C protease activity may be measured by any of the suitable methods known to those
25 skilled in the art, including in vivo and in vitro assays. An example of a suitable assay for activity measurements is the antiviral H1-HeLa cell culture assay described herein.

Administration of the compounds of the Formulas I to XII and their pharmaceutically acceptable prodrugs, salts, active metabolites, and solvates may be performed according to any of the generally accepted modes of administration available
30 to those skilled in the art. Illustrative examples of suitable modes of administration include oral, nasal, parenteral, topical, transdermal, and rectal.

- 76 -

An inventive compound of Formulas I to XII or a pharmaceutically acceptable salt, prodrug, active metabolite, or solvate thereof may be administered as a pharmaceutical composition in any pharmaceutical form recognizable to the skilled artisan as being suitable. Suitable pharmaceutical forms include solid, semisolid, liquid, or lyophilized formulations, such as tablets, powders, capsules, suppositories, suspensions, liposomes, and aerosols. Pharmaceutical compositions of the invention may also include suitable excipients, diluents, vehicles, and carriers, as well as other pharmaceutically active agents, depending upon the intended use or mode of administration. In preferred embodiments, the inventive pharmaceutical compositions are delivered orally, or intranasally in the form of suspensions. Acceptable methods of preparing suitable pharmaceutical forms of the pharmaceutical compositions may be routinely determined by those skilled in the art. For example, pharmaceutical preparations may be prepared following conventional techniques of the pharmaceutical chemist involving steps such as mixing, granulating, and compressing when necessary for tablet forms, or mixing, filling, and dissolving the ingredients as appropriate, to give the desired products for oral, parenteral, topical, intravaginal, intranasal, intrabronchial, intraocular, intraaural, and/or rectal administration.

The compounds (active ingredients) may be formulated into solid oral dosage forms which may contain, but are not limited to, the following inactive ingredients: diluents (i.e., lactose, corn starch, microcrystalline cellulose), binders (i.e., povidone, hydroxypropyl methylcellulose), disintegrants (i.e., crospovidone, croscarmellose sodium), lubricants (i.e., magnesium stearate, stearic acid), and colorants (FD&C lakes or dyes). Alternatively, the compounds may be formulated into other oral dosage forms including liquids, suspensions, emulsions, or soft gelatin capsules, with each dosage form having a unique set of ingredients.

Solid or liquid pharmaceutically acceptable carriers, diluents, vehicles, or excipients may be employed in the pharmaceutical compositions. Illustrative solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, sucrose, talc, gelatin, pectin, acacia, magnesium stearate, and stearic acid. Illustrative liquid carriers include syrup, peanut oil, olive oil, saline solution, and water. The carrier or diluent may include a suitable prolonged-release material, such as glyceryl monostearate or

- 77 -

glyceryl distearate, alone or with a wax. When a liquid carrier is used, the preparation may be in the form of a syrup, elixir, emulsion, soft gelatin capsule, sterile injectable liquid (e.g., solution), or a nonaqueous or aqueous liquid suspension. A dose of the pharmaceutical composition contains at least a therapeutically effective amount of the active compound (i.e., a compound of Formulas I to XII or a pharmaceutically acceptable salt, prodrug, active metabolite, or solvate thereof), and preferably is made up of one or more pharmaceutical dosage units. The selected dose may be administered to a mammal, for example, a human patient, in need of treatment mediated by inhibition of picornaviral 3C protease activity, by any known or suitable method of administering the dose, including: topically, for example, as an ointment or cream; orally; rectally, for example, as a suppository; parenterally by injection; or continuously by intravaginal, intranasal, intrabronchial, intraaural, or intraocular infusion. A "therapeutically effective amount" is intended to mean the amount of an inventive agent that, when administered to a mammal in need thereof, is sufficient to effect treatment for disease conditions alleviated by the inhibition of the activity of one or more picornaviral 3C proteases, such as human rhinoviruses, human poliovirus, human coxsackieviruses, encephalomyocarditis viruses, menigovirus, and hepatitis A virus. The amount of a given compound of the invention that will be therapeutically effective will vary depending upon factors such as the particular compound, the disease condition and the severity thereof, the identity of the mammal in need thereof, which amount may be routinely determined by artisans.

GENERAL SYNTHETIC METHODS

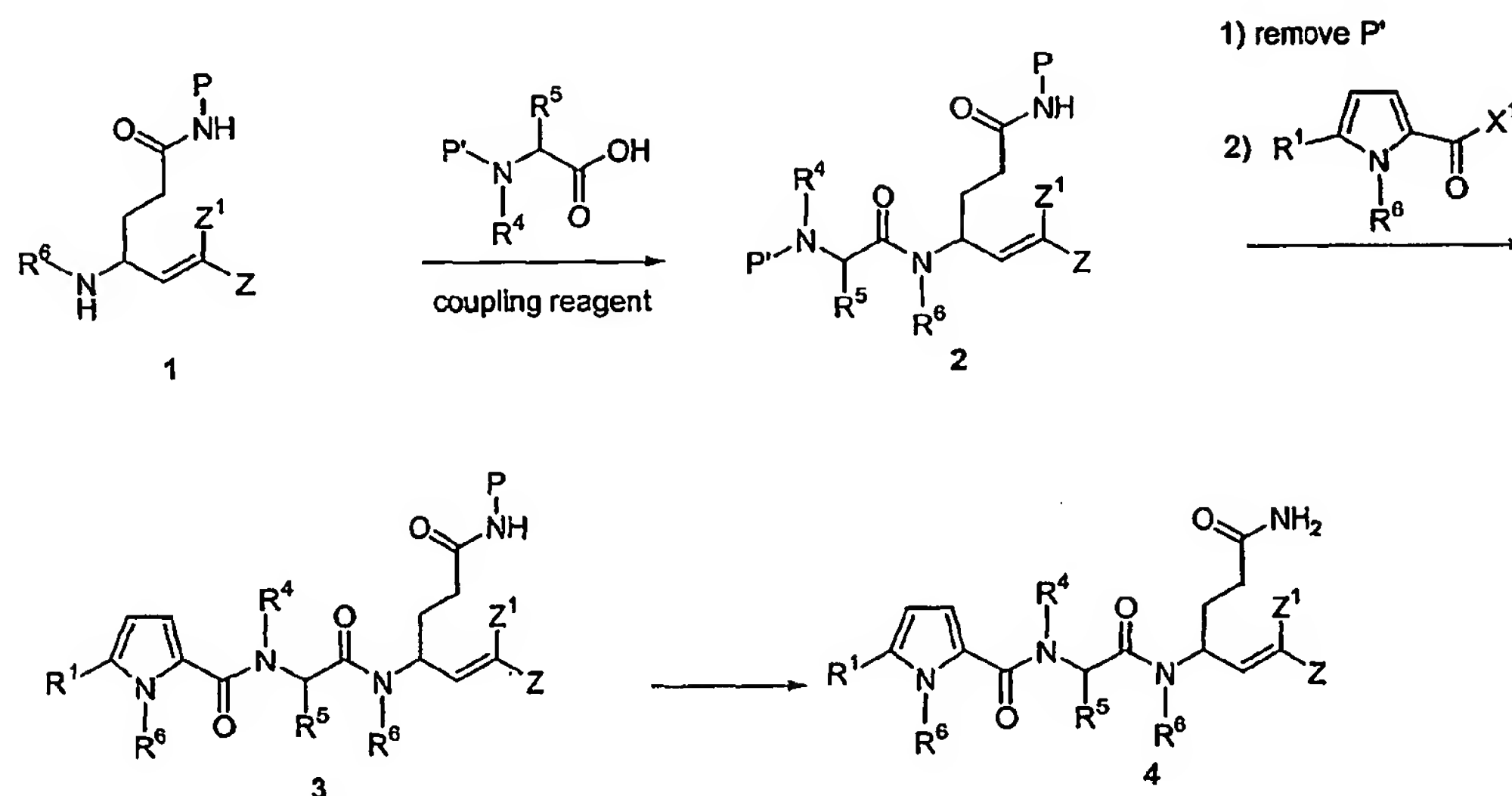
Preferably, compounds of the general formulas are prepared by the methods of the present invention, including the General Methods below, where the R^1 , R^4 , R^5 , R^6 , Z and Z^1 substituents present in the compounds illustrated in the General and Specific Methods are as defined above. Abbreviations used herein include: DCC (1,3-dicyclohexylcarbodiimide), HOBT (1-hydroxybenzotriazole hydrate), HATU (O-(7-azabenzotriazol-1-yl)-N,N,N',N' - tetramethyluronium hexafluorophosphate), IBX (2-iodoxybenzoic acid), Fmoc (9-fluorenylmethoxycarbonyl), Boc (t-butoxycarbonyl), DIEA (diisopropylethylamine), DMSO (dimethylsulfoxide), TMSOTf (trimethylsilyl

- 78 -

trifluoromethanesulfonate), TFA (trifluoroacetic acid), LiHMDS (lithium bis(trimethylsilyl)amide).

General Method 1

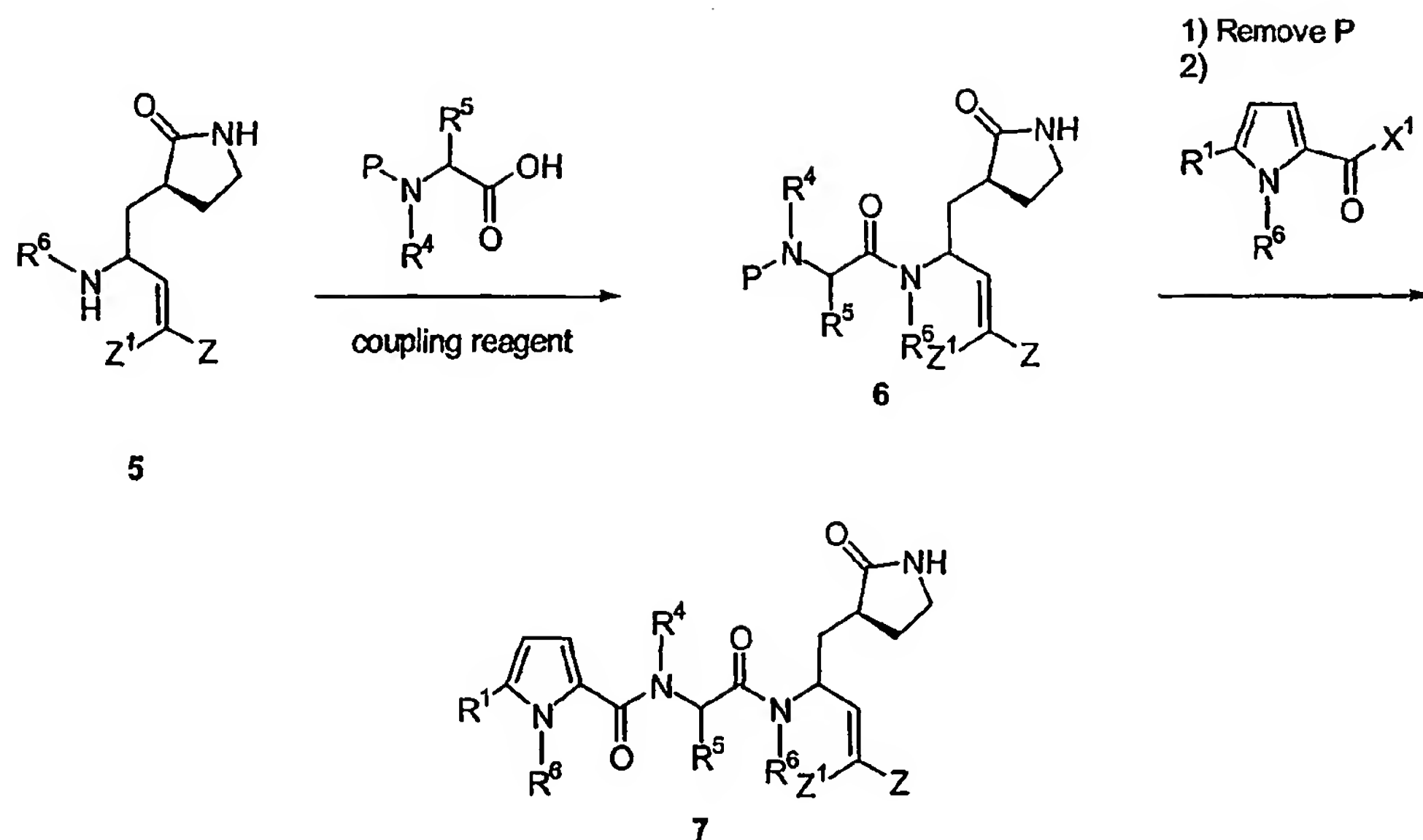
5



In General Method 1, a sidechain protected (P) compound 1 (Dragovich, et al., *J. Med. Chem.* 1998, 41, 2819), is coupled using standard peptide coupling methods, to another amino acid with a different protecting group (P') on the alpha-nitrogen, to give di-peptide compound 2. The P' protecting group is then selectively removed, and the resulting amine is coupled to a substituted pyrrole-2-carboxylic acid (prepared as described in General Methods 4, 5, and 6), or a suitably activated analog of this acid, such as an acid chloride, ester or amide (X¹ = OH, halo, etc.), to give 3. The sidechain-protecting group P is then removed to give 4. These compounds may also be made using solid phase synthetic techniques (Dragovich, et al., *Bioorg. Med. Chem.*, 1999 7, 589), where protecting group P constitutes a linker (such as the Rink linker) attached to solid phase resin.

- 79 -

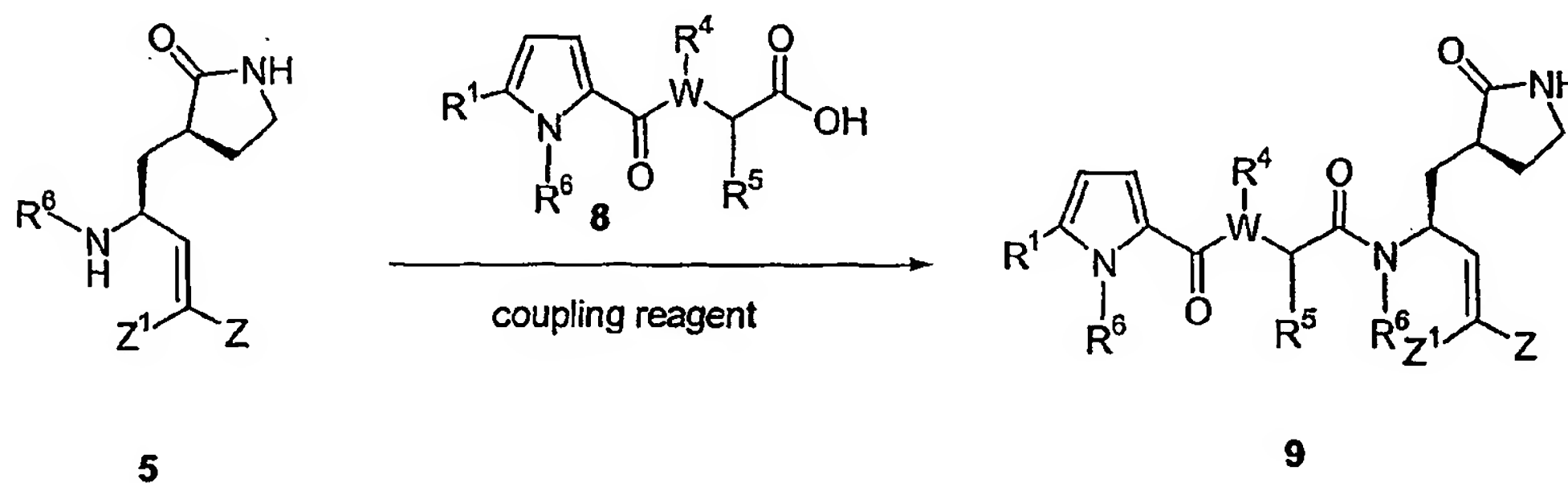
General Method 2



- 5 In General Method 2, compound 5 (prepared by a method analogous to that described in Tian, et al., U.S. Provisional Patent Application No. 60/150,358, filed August 24, 1999 (now U.S. Patent Application No. 09/643,864) and also Baldwin et al., *J. Org. Chem.*, 1971, 36, 1441) is coupled to another amino acid with sidechain protecting group P to give 6. The protecting group of 6 is removed, and the liberated
- 10 amine is coupled to a 5-substituted pyrrole-2-carboxylic acid (prepared as described in General Methods 4, 5, and 6) via a suitably activated analog of this acid, such as an acid chloride, ester or amide (X¹ = OH, halo, etc.), to give compound 7.

- 80 -

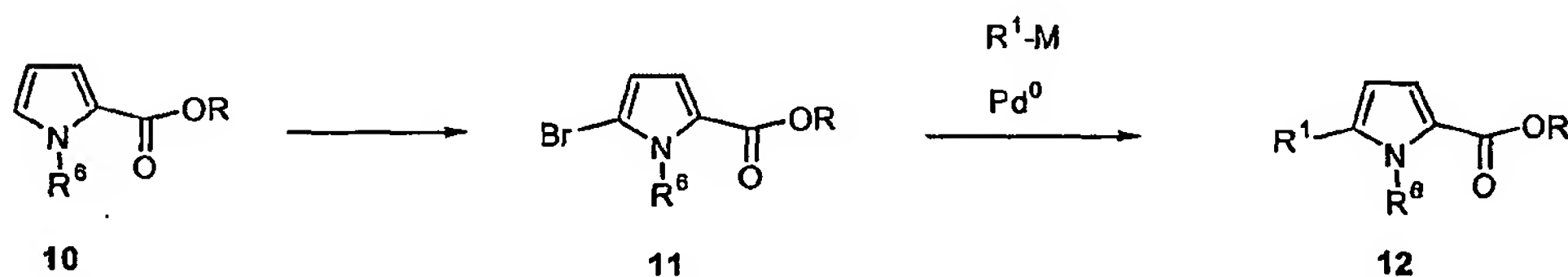
General Method 3



5 In General Method 3, compound 5 is coupled to carboxylic acids of the type 8 (prepared as described in General Methods 7 and 8), where $W = N$ or CH , to give compound 9.

General Method 4

10

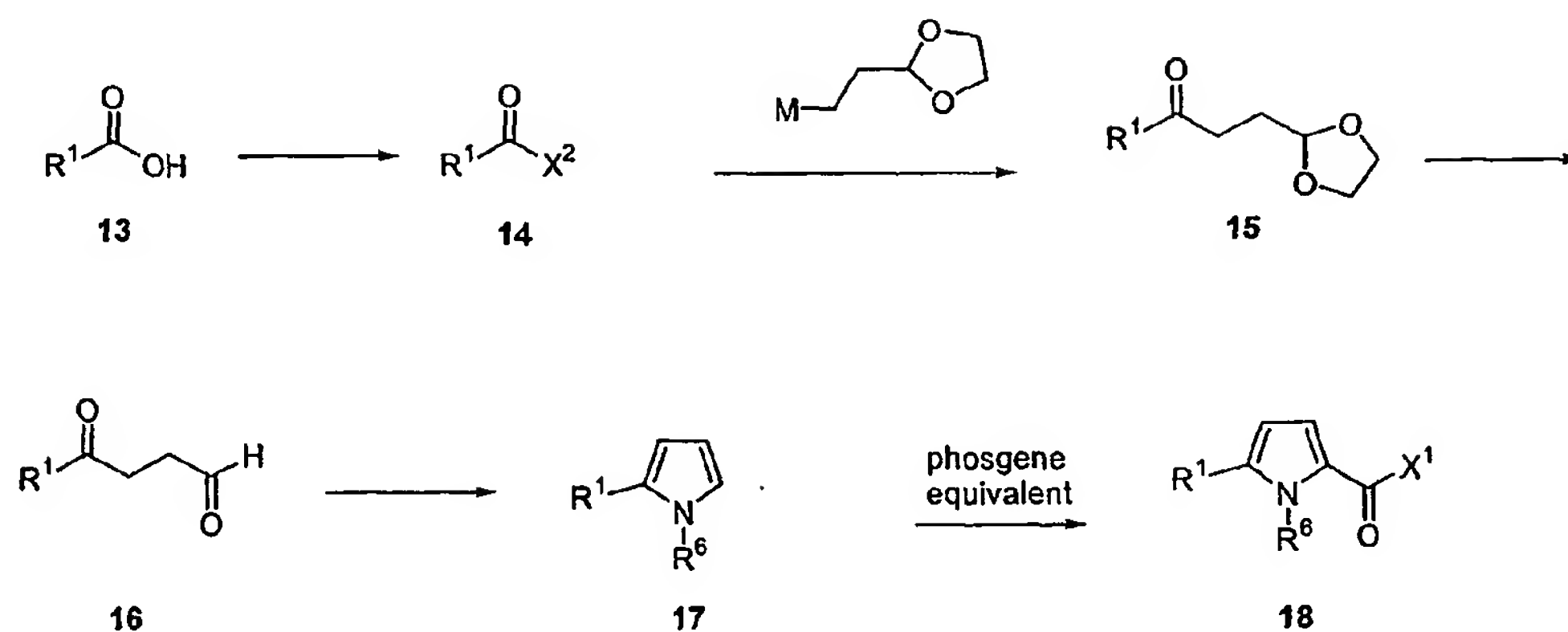


15

In General Method 4, 2,5-disubstituted pyrroles are prepared by bromination of pyrrole-2-carboxylic acid ester 10, where R is an alkyl or aryl group, which is unsubstituted or substituted with one or more suitable substituents, to give 11, followed by a transition-metal mediated carbon-carbon bond forming reaction (for example, using Pd^0 with an appropriate ligand such as triphenylphosphine or triphenylarsine) with an organometallic species, R^1M (for example, an organoboronic acid or an organotin compound) to give 12.

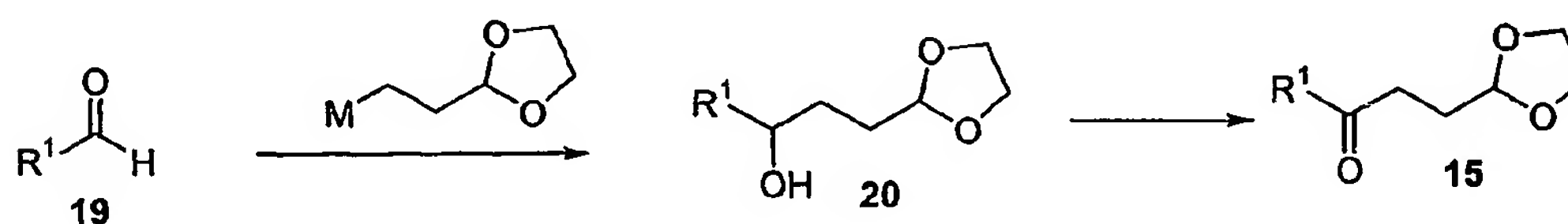
20

General Method 5



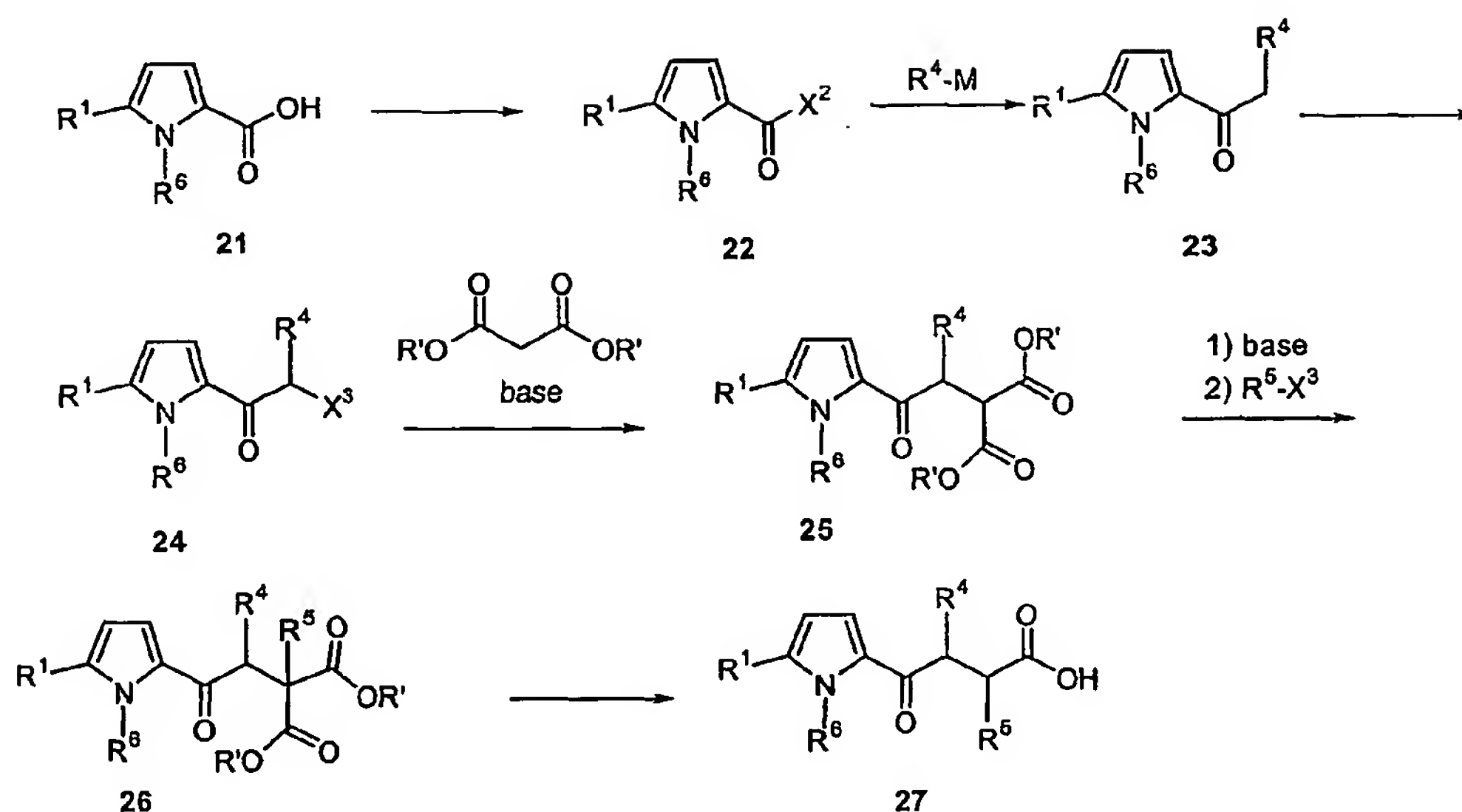
5 General Method 5 depicts another method used to make 2,5-disubstituted
pyrroles, analogous to the method described by Kruse, et al., *Heterocycles*, 1987, 26,
3141. A carboxylic acid 13 is converted to a suitably activated species 14 ($X^2 =$ a
Weinreb amide ($-N(OCH_3)CH_3$), halo, etc.) then reacted with a nucleophilic
organometallic compound containing a protected aldehyde to provide 15. The aldehyde
10 is deprotected to give 16, then is condensed with an ammonia equivalent such as
ammonium chloride, to provide pyrrole 17. This pyrrole is then reacted with a
phosgene-type equivalent such as trichloroacetyl chloride (analogous to the method
described by Bailey, et al., *Org. Synth.*, 1971, 51, 100), to provide the 2,5-disubstituted
pyrrole 18. ($X^1 = OH$, halo, etc.).

General Method 6



20 General Method 6 shows an alternate method to make 2,5-disubstituted pyrroles. Aldehyde 19 is reacted with a nucleophilic organometallic compound containing a protected aldehyde to provide alcohol 20. The alcohol is then oxidized to ketone 15 using standard methodology such as a Swern oxidation. Ketone 15 is carried on to pyrrole 18 using the same method as shown in General Method 5.

General Method 7

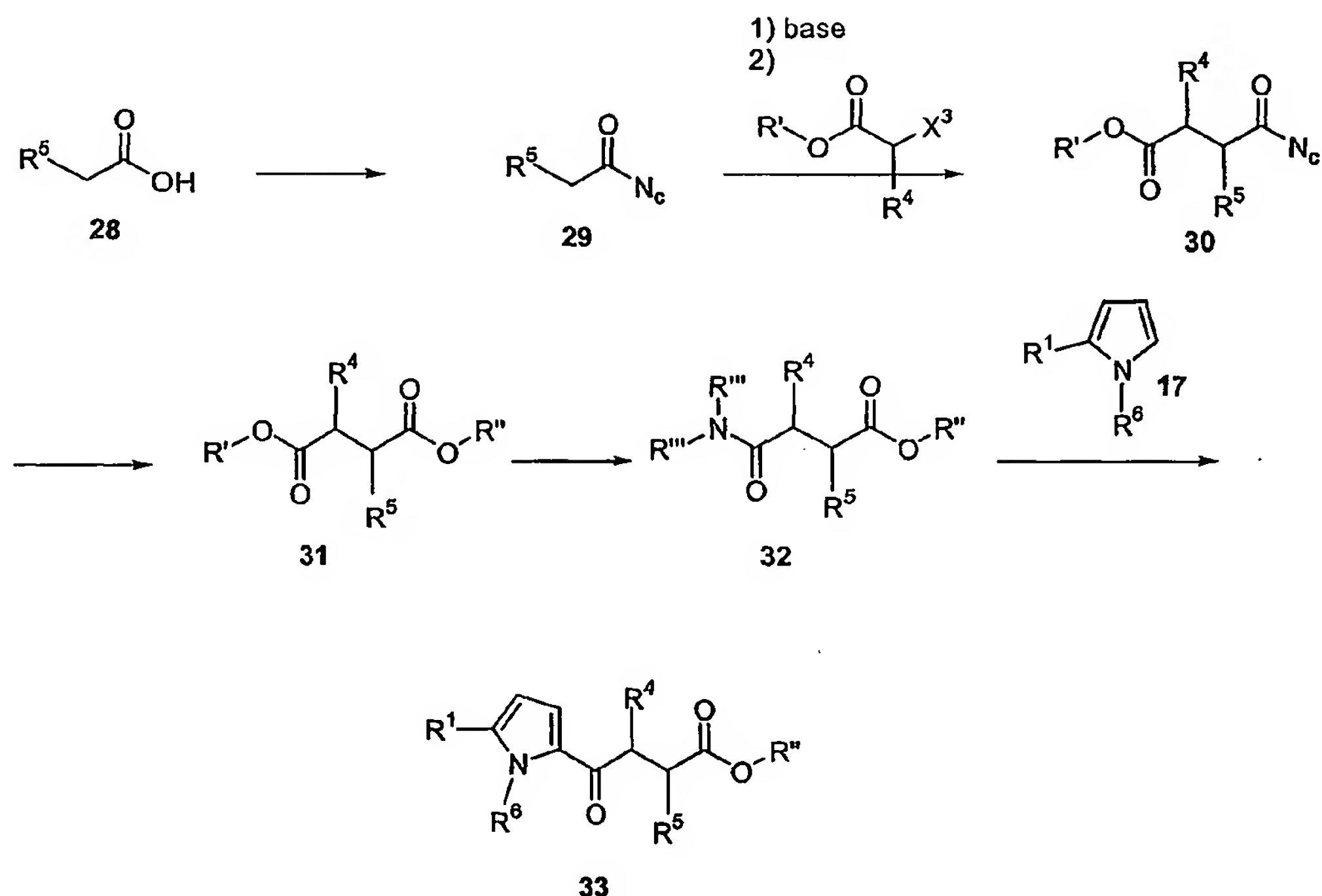


5

General Method 7 depicts the preparation of a pyrrole containing the keto-methylene moiety, **27**, analogous to the method described by Gonzalez-Muniz et. al. (Gonzalez-Muniz, et al., *Tetrahedron*, 1992, 48, 5191; Garcia-Lopez, et al., *Tetrahedron Lett.*, 1988, 29, 1577; Garcia-Lopez, et al., *Tetrahedron*, 1988, 44, 5138). Carboxylic acid **21** is converted to a suitably reactive intermediate **22** such as a Weinreb amide, acid chloride or ester ($X^2 = N(OCH_3)CH_3$, halo, etc.), then reacted with an organometallic reagent (R^4M , such as methyllithium) to give pyrrole-acetone compound **23**. This compound is then halogenated to give **24** (where $X^3 = \text{halo}$), then reacted with a malonate salt ($R' = \text{alkyl}$) to give **25**. This compound is deprotonated by treatment with a strong base, then reacted with an electrophile (R^5-X^3) to give **26**. Decarboxylation of compound **26** gives product **27**.

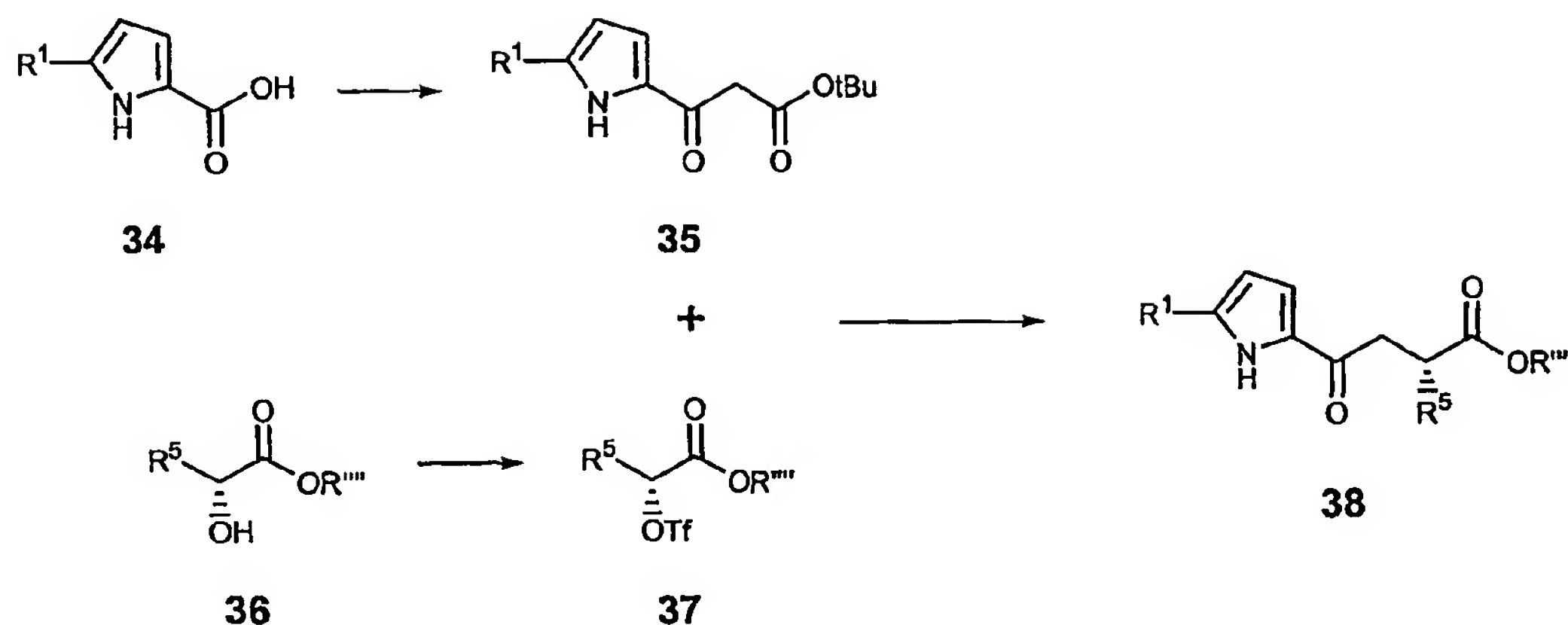
15

General Method 8



- 5 General Method 8 shows the preparation of an optically active pyrrole containing the keto-methylene moiety, compound 33. Carboxylic acid 28 is converted to chiral amide 29, by coupling to a chiral amine or oxazolidinone, N_c , that is known to control enolate alkylation diastereoselectivity. Compound 29 is deprotonated, then reacted with an electrophile such as t-butyl bromoacetate, analogous to the method described by Charlton, et al., *Can. J. Chem.* 1997, 75, 1076, to give 30. The chiral auxiliary is removed, and the resulting acid is esterified to give 31. The R' ester of 31 is selectively removed, and the resulting acid is converted to the disubstituted amide 32, by coupling to a secondary amine. Compound 32 is reacted with pyrrole 17, under typical Vilsmeier reaction conditions (Silverstein, et al., *Org. Synth.*, 1963, *Coll. Vol. IV*, 831) to give pyrrole 33. As used herein, R' , R'' and R''' are each independently lower alkyl, which is unsubstituted or substituted with one or more suitable substituents, .

General Method 9



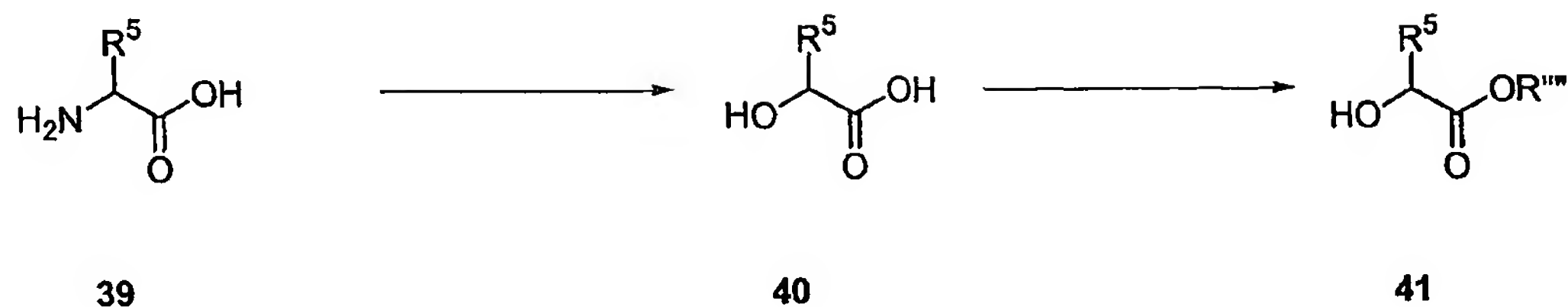
5

In General Method 9, a pyrrole-carboxylic acid 34 (commercially available or prepared by methods described in the chemical literature or as prepared as described in General Methods 4, 5 and 6), where R¹ is as defined above, is transformed into ketoester 35. Compound 35 is subsequently deprotonated and coupled with triflate 37 (which incorporates R⁵ and which can be prepared from hydroxy-ester 36, where R^{'''} is alkyl or cycloalkyl, e.g., lower alkyl, allyl, benzyl, or C₃-C₆ cycloalkyl, which are unsubstituted or substituted with one or more suitable substituents) to afford intermediate 38 after acid-effected decarboxylation. Intermediate 38 is related to compound 32 (General Method 8) and may be utilized in any of the previously described general syntheses where appropriate. Note that the NH present in pyrrole-carboxylic acid 34 may also be protected with a suitable protecting group which may be removed at any time during the synthesis of 38. The methodology for converting pyrrole-carboxylic acid 34 to intermediate 38 is generally described in: Hoffman, R. V.; Tao, J. *Tetrahedron* 1997, 53, 7119-7126.

20

- 85 -

General Method 10



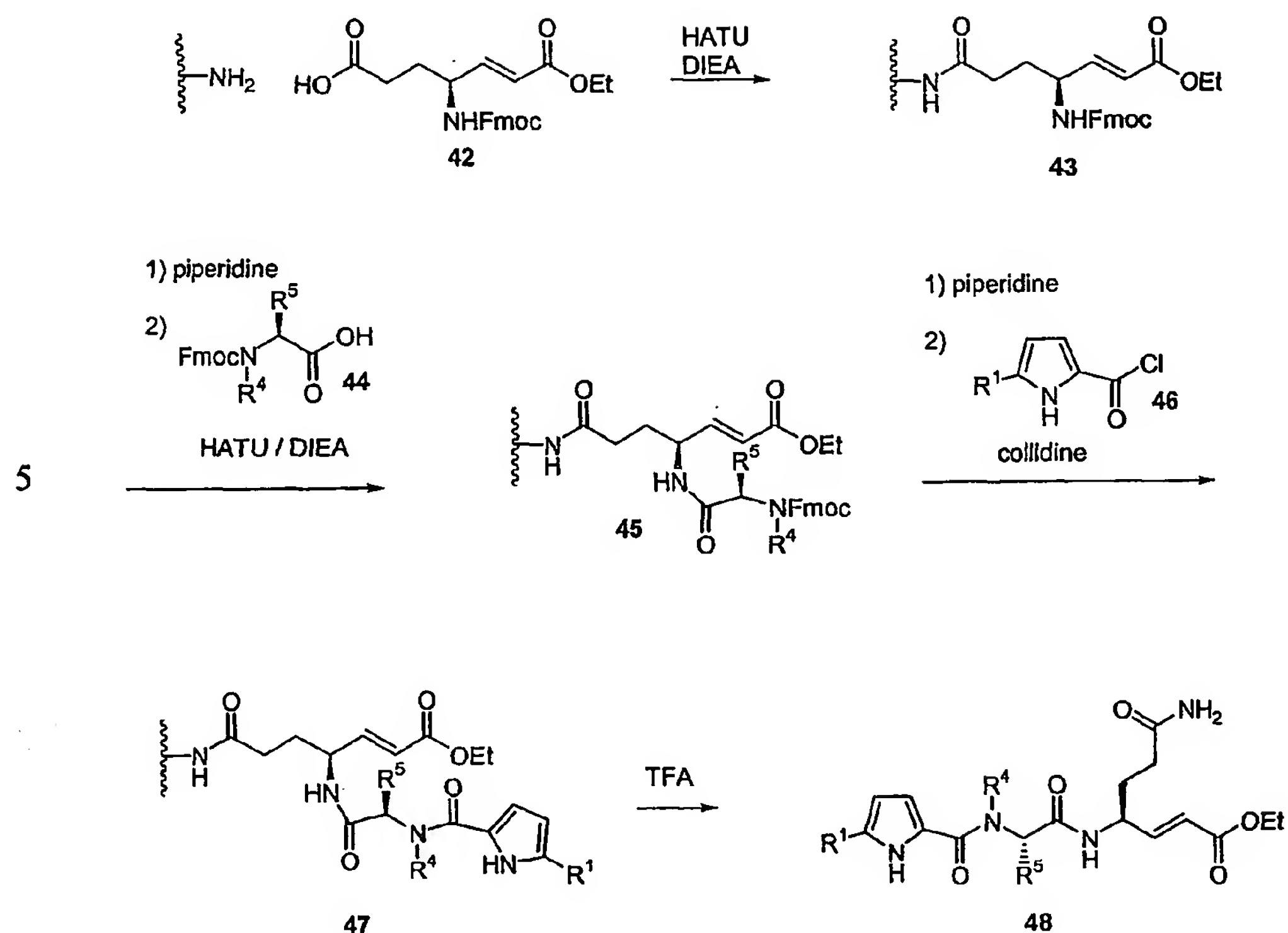
5

In General Method 10, an amino acid 39 (or salt thereof) which incorporates R^5 is transformed into hydroxy acid 40. This intermediate is subsequently converted to hydroxy ester 41 which may be utilized in General Method 9 above for the preparation of the compounds described in this invention.

10

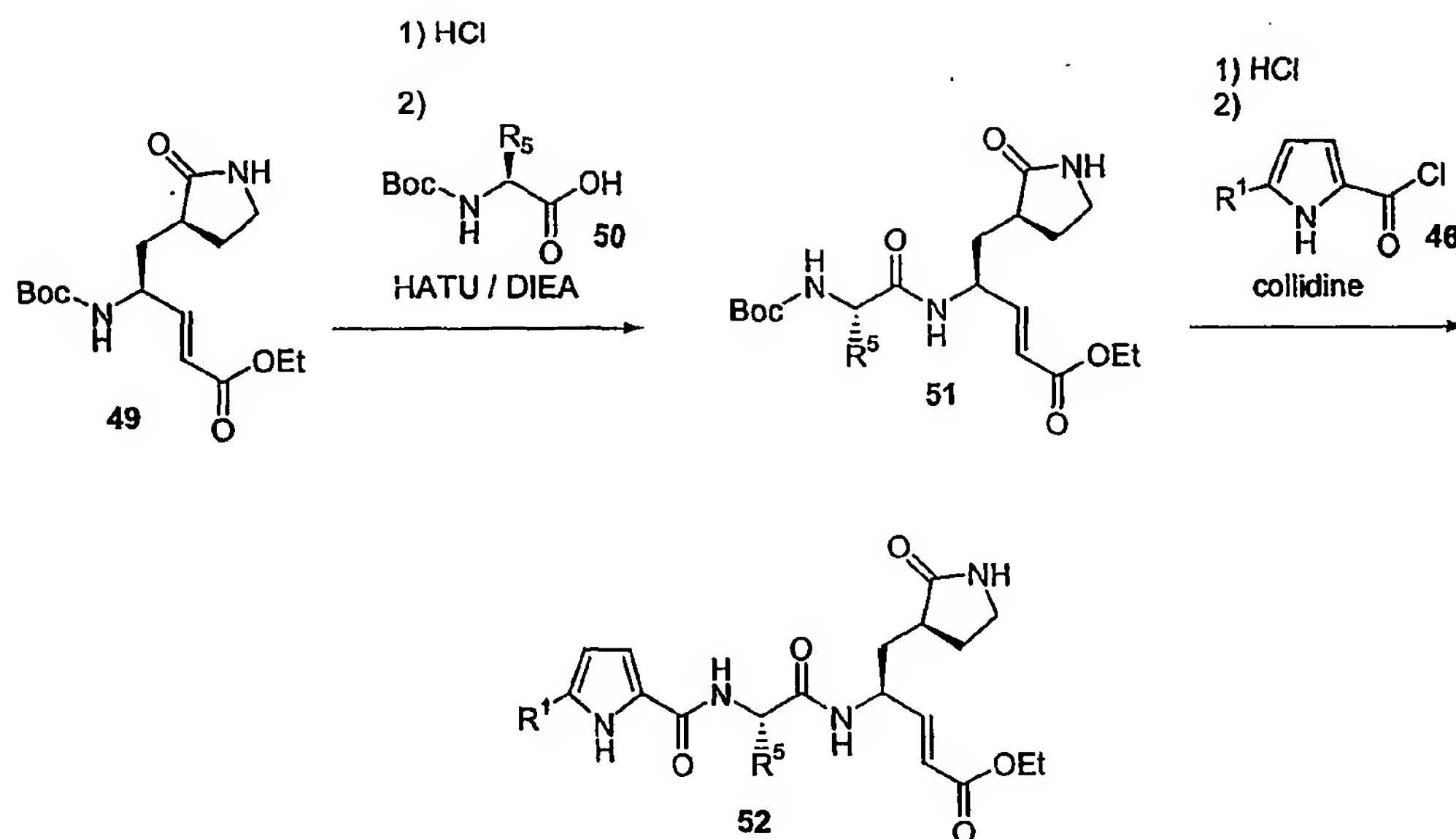
SPECIFIC METHODS

Specific Method 1



Specific Method 1 describes the preparation of compounds containing a glutamine residue in the P-1 position. Fmoc-4-amino-hept-2(trans)-enedioic acid –1
 10 ethyl ester 42 (Dragovich, et al., *J. Med. Chem.* 1998, 41, 2819) was coupled to Rink polystyrene utilizing HATU as a coupling reagent to get 43. The Fmoc protecting group was removed with piperidine, and the liberated amine was then coupled to an Fmoc-protected amino acid 44 to get compound 45. The Fmoc of 45 was again removed with piperidine, and the free amine was acylated with a 5-substituted-2-
 15 pyrrole carboxylic acid chloride 46 (prepared as described in Specific Methods 4,5, and 6). The final compound, 37, was cleaved from the resin with trifluoroacetic acid, to give compound 48.

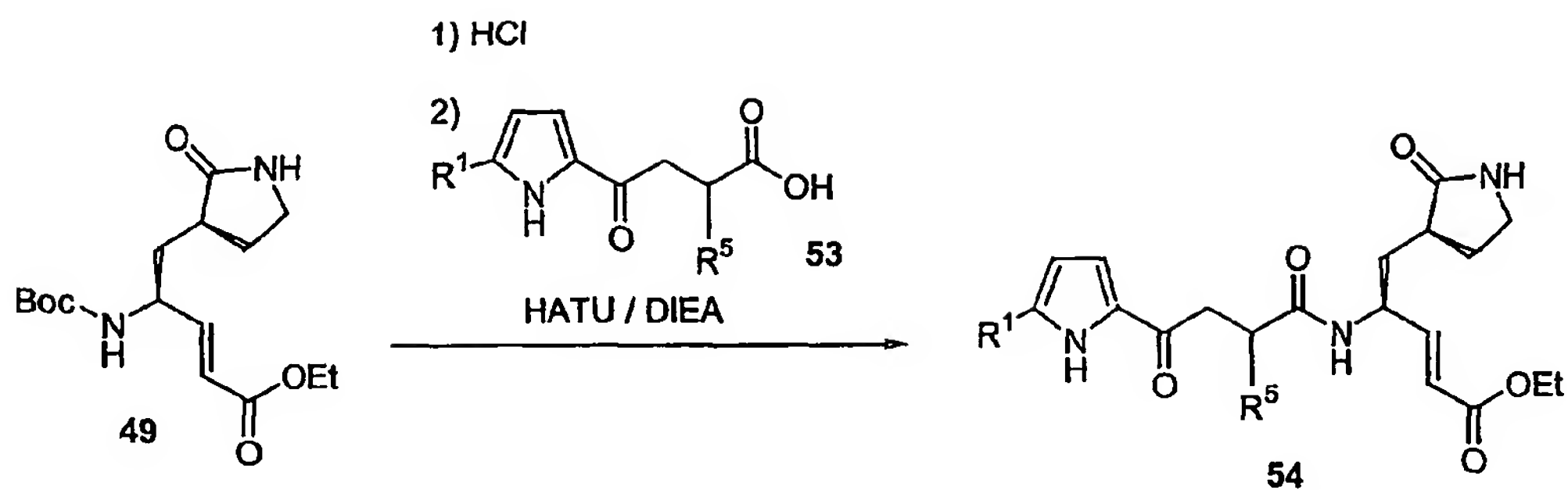
Specific Method 2



- 5 Specific Method 2 describes the synthesis of compounds containing the oxo-pyrrolidine sidechain in the P-1 position. Boc-protected 4S-amino-5-(2-oxo-pyrrolidin-3S-yl)-pent-2(trans)-enoic acid ethyl ester 49 (prepared by a method analogous to that described in Tian, et al., U.S. Provisional Patent Application No. 60/150,358, filed August 24, 1999 and also Baldwin et al., *J. Org. Chem.*, 1971, 36, 1441) was
- 10 deprotected with HCl, then coupled using HATU to a Boc-protected amino acid 50. The Boc-protected product 51 was treated with HCl, then coupled to a 5-substituted-pyrrole-2-carboxylic acid chloride 46 (prepared as described in Specific Methods 4, 5, and 6), to produce product 52.

- 88 -

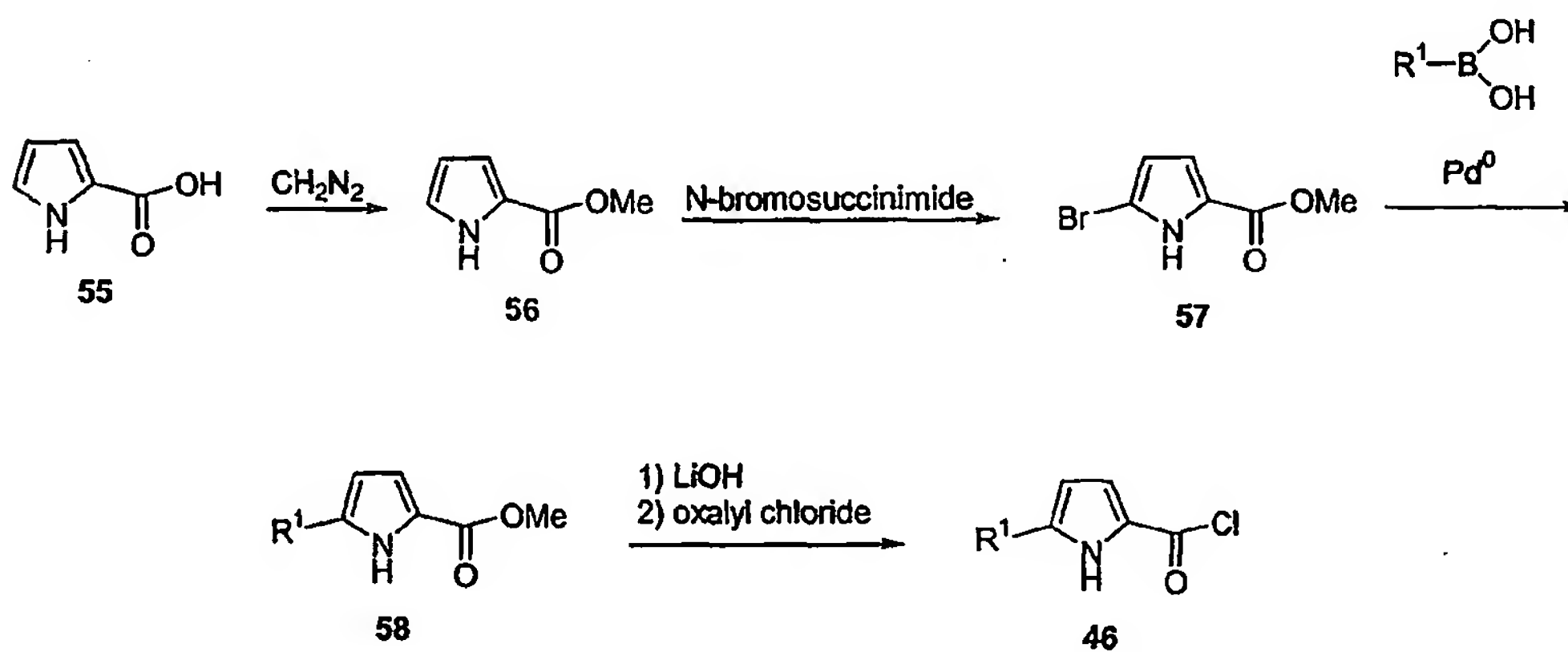
Specific Method 3



5 Specific Method 3 describes the preparation of compounds containing the pyrrole-ketomethylene moiety. Boc-protected 4S-amino-5-(2-oxo-pyrrolidin-3S-yl)-pent-2(trans)-enoic acid ethyl ester 49 was deprotected with HCl, then coupled to acid 53 (prepared as described in Specific Method 7 and 8), using HATU, to provide compound 54.

10

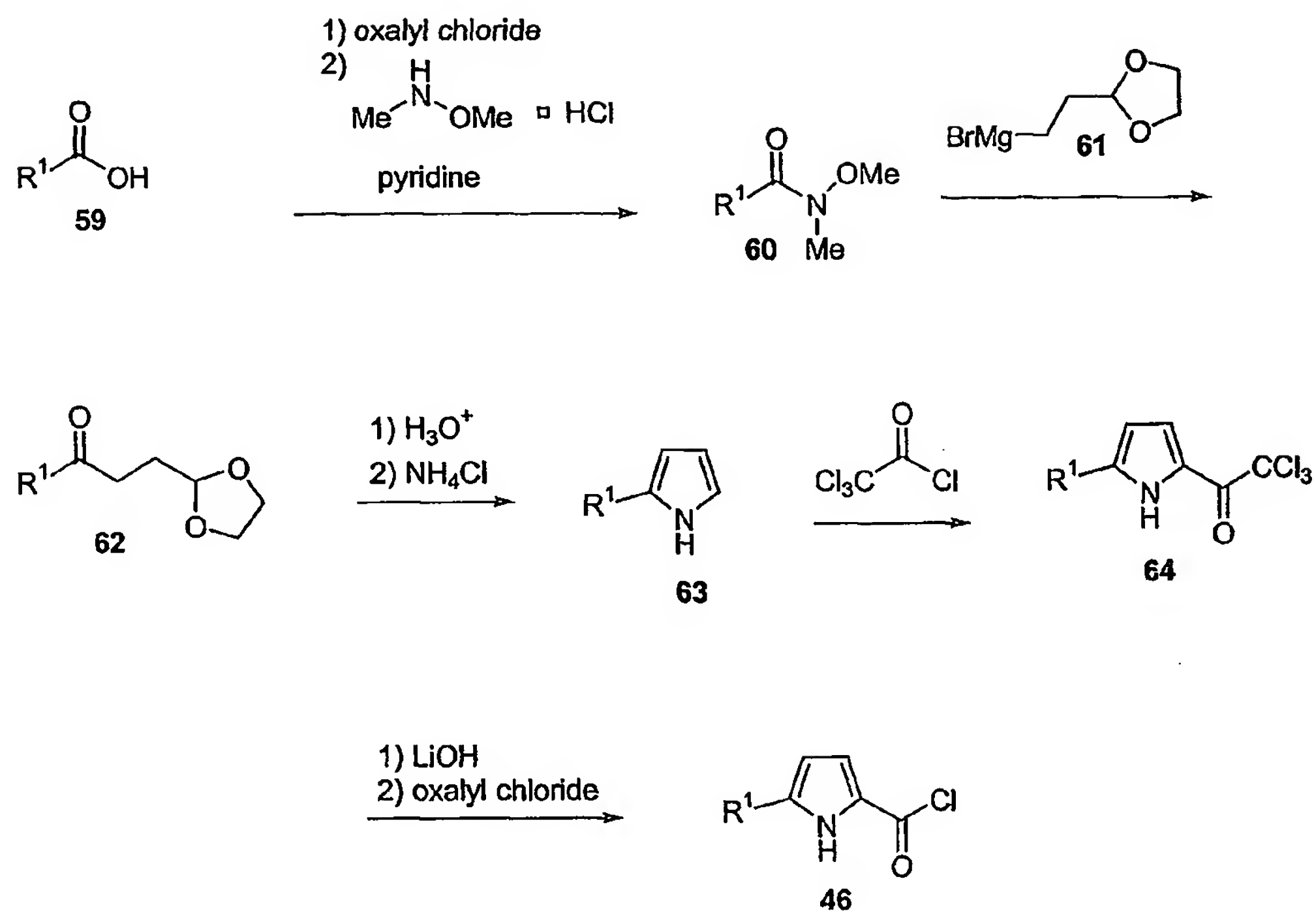
Specific Method 4



15 Specific Method 4 describes the synthesis of 5-substituted-pyrrole-2-carboxylic acid chlorides. Pyrrole-2-carboxylic acid 55 was esterified with diazomethane, to give methyl ester 56, then brominated with N-bromosuccinimide to give 5-bromopyrrole 57. The bromide was reacted with a boronic acid using standard Suzuki coupling conditions to give 58. The methyl ester was cleaved with lithium hydroxide, and the resulting acid was converted to the acid chloride 46 using oxalyl chloride.

20

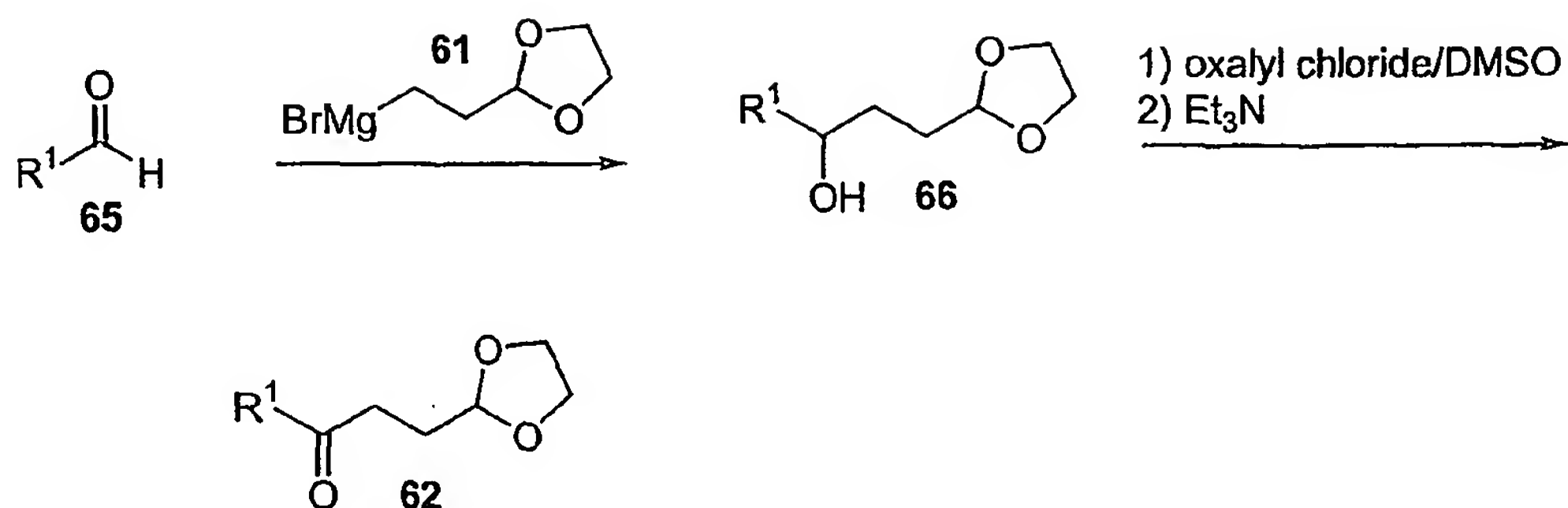
Specific Method 5



Specific Method 5 describes an alternate method of pyrrole synthesis. Carboxylic acid 59 was converted to an acid chloride using oxalyl chloride, then converted to the N-methoxy-N-methyl amide with O,N-dimethyl hydroxylamine. This amide 60 was reacted with Grignard reagent 61 to give ketone 62. The dioxolane-protecting group was converted to the corresponding aldehyde with aqueous HCl, then condensed with ammonium chloride to give pyrrole 63. This pyrrole was reacted with trichloroacetyl chloride to give the disubstituted pyrrole 64, which was then hydrolyzed to the corresponding carboxylic acid with lithium hydroxide, then converted to the acid chloride 46 using oxalyl chloride.

- 90 -

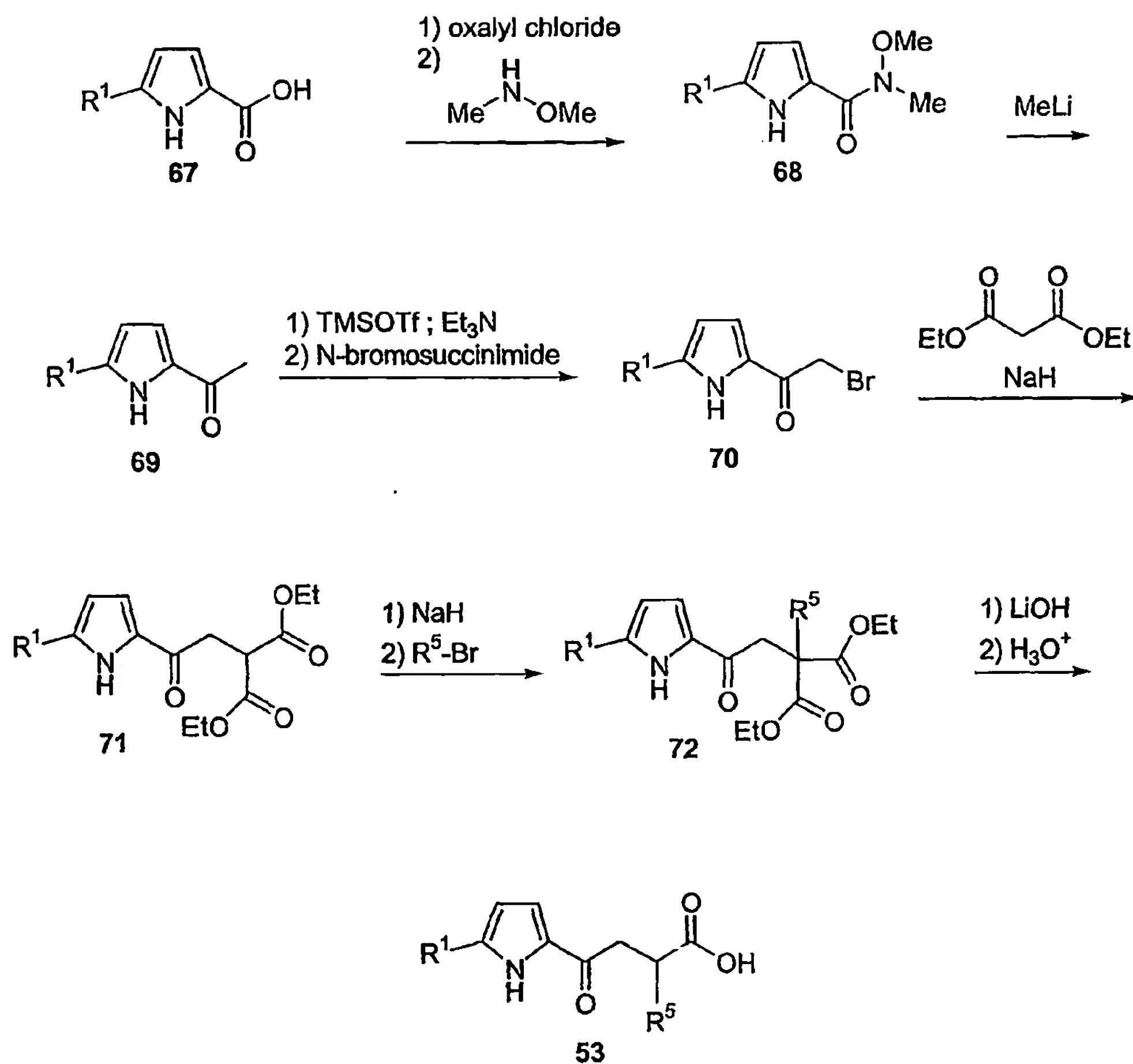
Specific Method 6



5

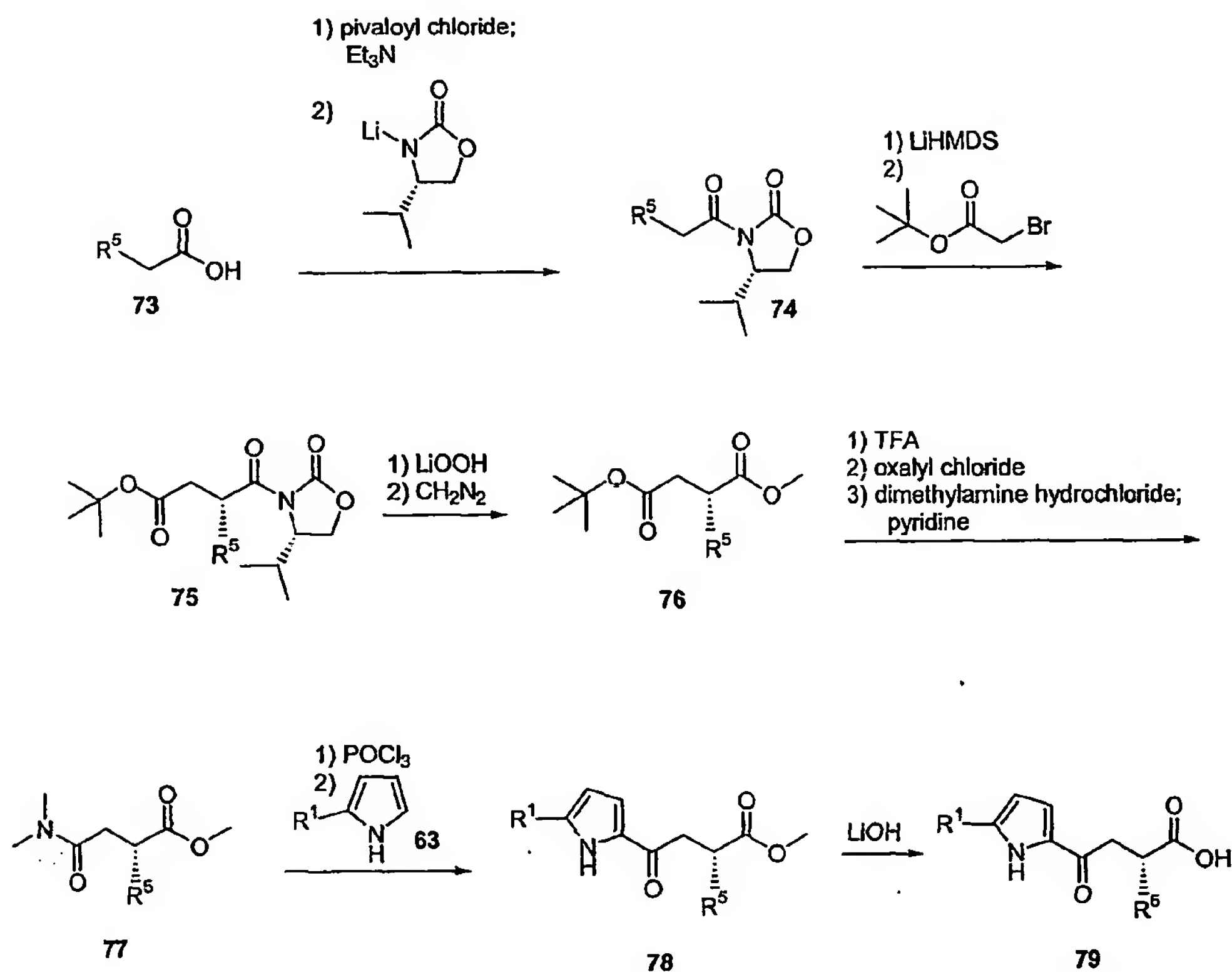
Specific Method 6 describes an alternate method of pyrrole synthesis. Aldehyde **65** was reacted with Grignard reagent **61** to give alcohol **66**. This alcohol was subjected to Swern oxidation conditions to provide ketone **62**, which was converted to the acid chloride **46** according to Specific Method 5.

Specific Method 7



- 5 Specific Method 7 describes the synthesis of a racemic pyrrole-ketomethylene compound. 5-Substituted-pyrrole-2-carboxylic acid **67** (prepared as described in Specific Methods 4, 5 and 6) was converted to the Weinreb amide **68** using standard conditions, then treated with methyllithium to give pyrrole-acetone **69**. This ketone was converted to its silyl-enol ether with trimethylsilyl triflate, then brominated with N-
- 10 bromosuccinimide to give bromide **70**. The bromide was displaced with sodium diethylmalonate to give malonate **71**. The sodium enolate of this compound was alkylated to give **72**, which was then de-esterified and de-carboxylated to give carboxylic acid **53**.

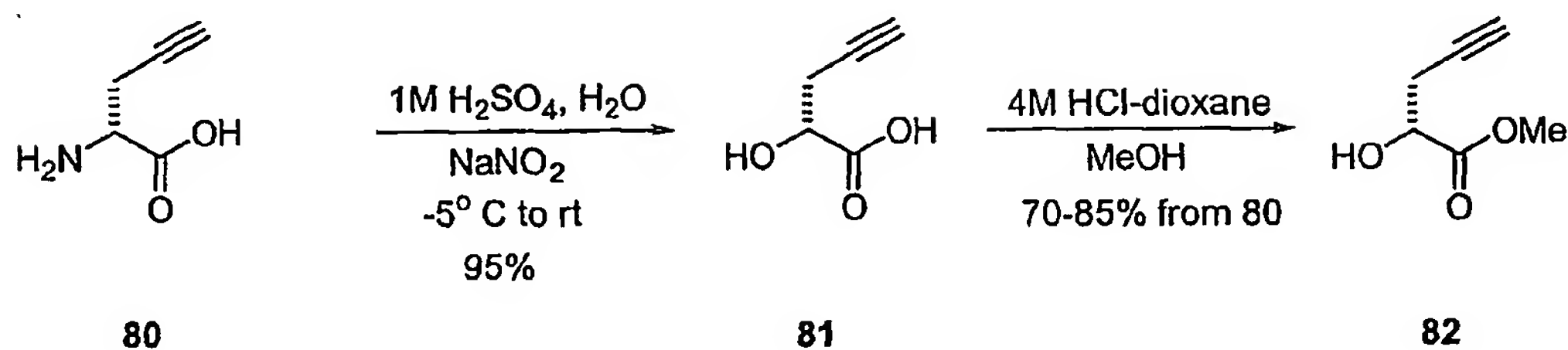
Specific Method 8



- 5 Specific Method 8 describes the enantioselective preparation of a pyrrole-ketomethylene compound. Carboxylic acid **73** was converted to the chiral amide **74** using standard conditions, then converted to its lithium enolate and alkylated with t -butylbromoacetate to give **75**. The chiral auxiliary was removed with lithium hydroperoxide, and the resulting acid was esterified with diazomethane to give ester **76**.
- 10 The t -butylester was selectively removed with trifluoroacetic acid, and the resulting acid was converted to dimethyl amide **77** by treatment of the acid chloride (formed using oxalyl chloride) with dimethylamine hydrochloride. Amide **77** was reacted with pyrrole **63** (prepared as described in Specific Methods 4,5 and 6) using standard Vilsmeier conditions to give pyrrole-ketomethylene **78**. The methyl ester was cleaved
- 15 with lithium hydroxide to give carboxylic acid **79**.

- 93 -

Specific Method 9

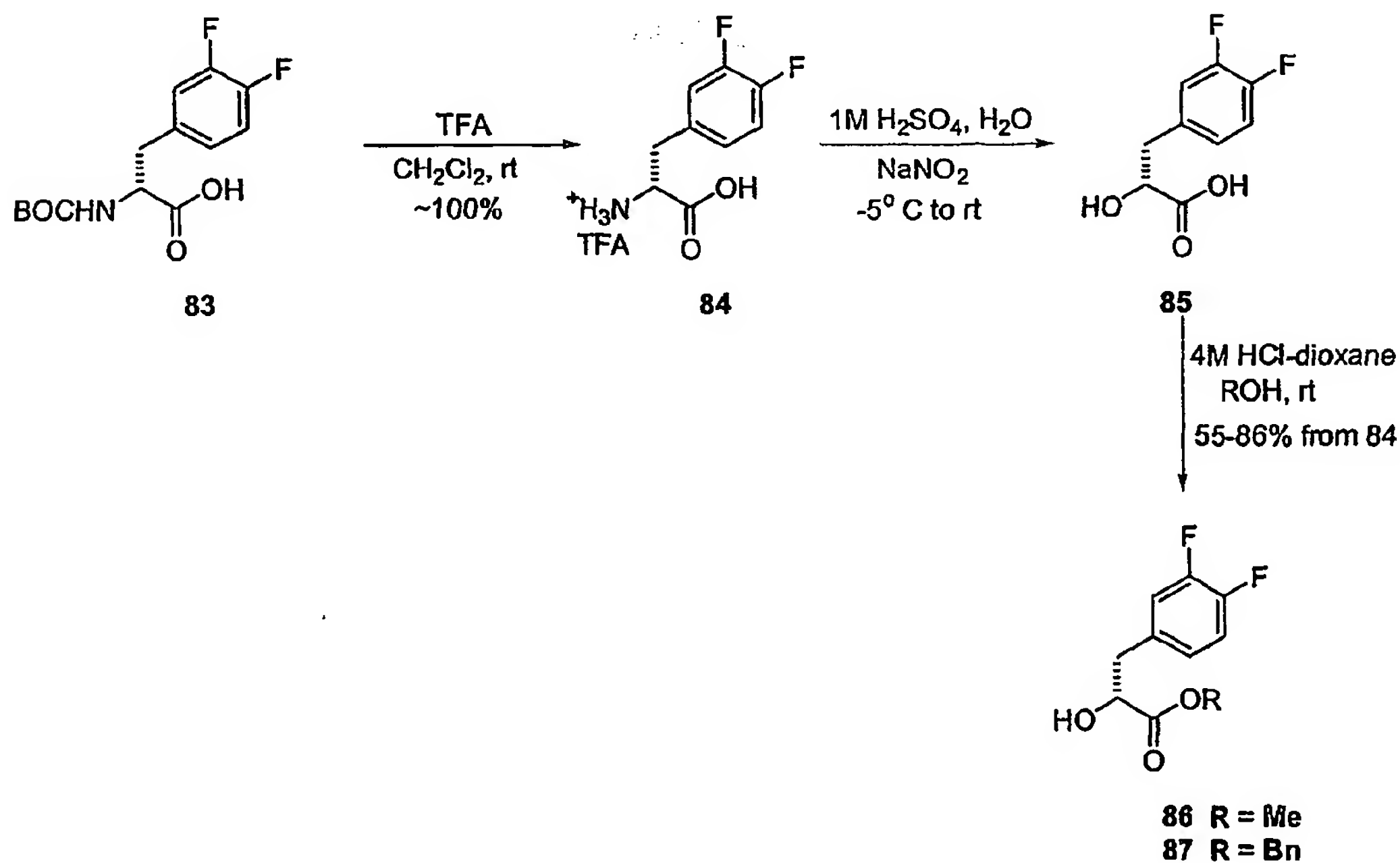


5

In Specific Method 9, H-D-propargyl glycine (80) (or a suitable salt thereof) is treated with sodium nitrite under mildly acidic aqueous conditions to provide hydroxy acid 81 in good yield. This material is esterified by exposure to acidic methanol to give hydroxy ester 82.

10

Specific Method 10



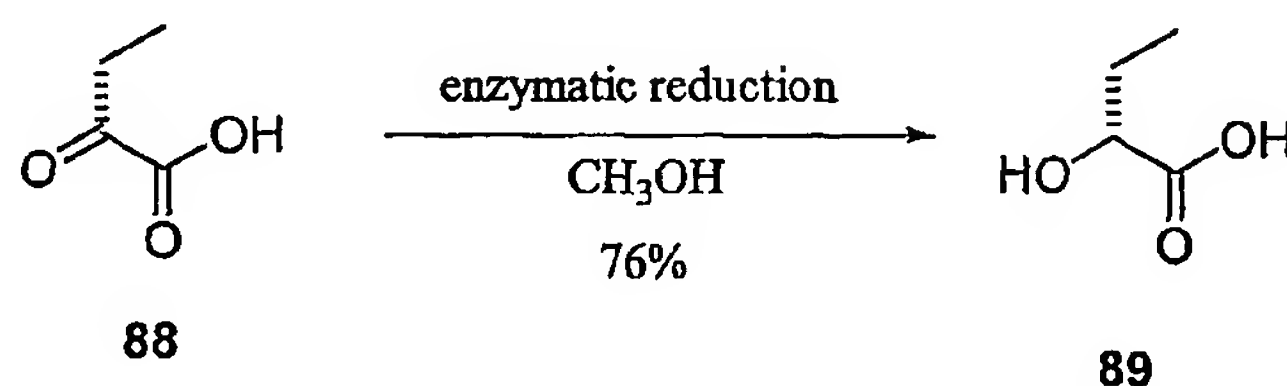
15

In Specific Method 10, Boc-D-3,4-difluorophenylalanine 83 is deprotected by treatment with trifluoroacetic acid in CH_2Cl_2 to afford amino acid TFA salt 84. This intermediate is treated with sodium nitrite under mildly acidic aqueous conditions to

- 94 -

provide hydroxy acid 85 in good yield. Compound 85 is esterified by exposure to either methanol or benzyl alcohol under acidic conditions to give hydroxy esters 86 and 87, respectively.

5 Specific Method 11



10 In Specific Method 11, 2-ketobutyric acid (88) is subjected to an enzyme-mediated reduction process to afford hydroxy acid 89 in good yield.

EXAMPLES

15 Examples of the processes used to make several of the compounds of Formulas I and II are set forth below. The structures of the compounds of the following examples were confirmed by one or more of the following: proton magnetic resonance spectroscopy, infrared spectroscopy, elemental microanalysis and melting point. Proton magnetic resonance (¹H NMR) spectra were determined using either a Varian
20 UNITYplus 300 or a General Electric QE-300 spectrometer operating at a field strength of 300 megahertz (MHz). Chemical shifts are reported in parts per million (ppm, δ) downfield from an internal tetramethylsilane standard. Alternatively, ¹H NMR spectra were referenced to residual protic solvent signals as follows: CHCl₃ = 7.26 ppm; DMSO = 2.49 ppm, C₆H₅ = 7.15 ppm. Peak multiplicities are designated as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; br, broad resonance; m, multiplet. Coupling constants are given in Hertz. Infrared absorption (IR) spectra
25 were obtained using a Perkin-Elmer 1600 series FTIR spectrometer. Elemental microanalyses were performed by Atlantic Microlab Inc., Norcross, GA and gave results for the elements stated within ±0.4% of the theoretical values. Flash column chromatography was conducted using Silica gel 60 (Merck Art 9385). Analytical thin layer chromatography (TLC) was conducted using precoated sheets of Silica 60 F254

- 95 -

(Merck Art 5719). Melting points were determined on a Mel-Temp apparatus and are uncorrected. All reactions were conducted in septum-sealed flasks under a slight positive pressure of argon unless otherwise noted. All commercial reagents were used as received from their respective suppliers with the following exceptions.

- 5 Tetrahydrofuran (THF) was distilled from sodium-benzophenone ketyl prior to use. Dichloromethane (CH₂Cl₂) was distilled from calcium hydride prior to use. The abbreviations used herein include: Et₂O (diethyl ether), DMF (N,N-dimethylformamide), DMSO (dimethylsulfoxide), MTBE (tert-butyl methyl ether), CH₃OH (methanol), EtOH (ethanol), EtOAc (ethyl acetate), DME (ethylene glycol dimethyl ether) Ac (acetyl), Me (methyl), Ph (phenyl), Tr (triphenylmethyl), Cbz (benzyloxycarbonyl), Boc (tert-butoxycarbonyl), TFA (trifluoroacetic acid), DIEA (N,N-diisopropylethylamine), TMEDA (N,N,N',N'-tetramethylethylenediamine), AcOH (acetic acid), Ac₂O (acetic anhydride), NMM (4-methylmorpholine), HOBt (1-hydroxybenzotriazole hydrate), HATU (O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate), EDC (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride), DCC (dicyclohexyl-carbodiimide), DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone), DMAP (4-dimethylaminopyridine), Gln (glutamine), Leu (leucine), Phe (phenylalanine), Phe(4-F) (4-fluorophenylalanine), Val (valine), amino-Ala (2,3-diaminopropionic acid), and (S)-Pyrrol-Ala((2S,3'S)-2-amino-3-(2'-oxopyrrolidin-3'-yl)-propionic acid). Additionally, "L" represents the configuration of naturally occurring amino acids.
- 10
15
20

EXAMPLE 1

Preparation of Gln-resin and Phe-Gln resin

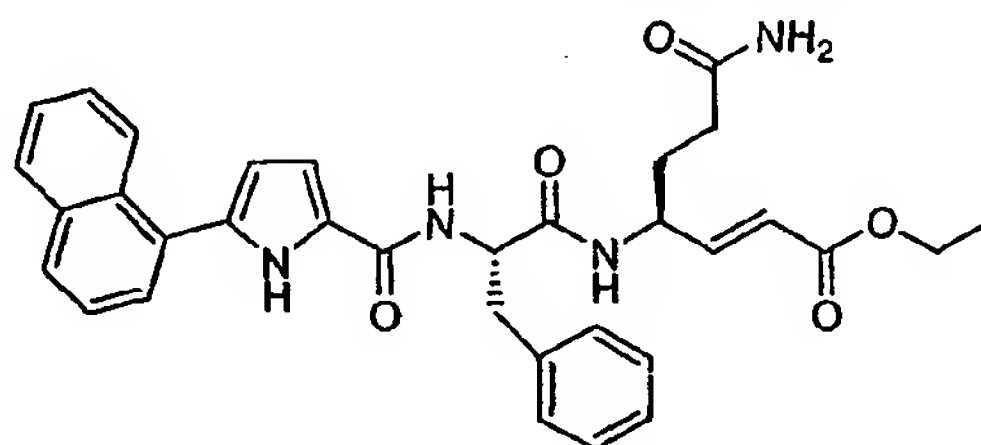
- 25 Fmoc-Rink polystyrene resin (1.58 mmol, 2.40 g) was treated with a 1:1 solution of DMF-piperidine (25 ml) in a shaker vessel, to remove the Fmoc. The resulting slurry was agitated for 15 min, then washed with DMF (3x10 ml). The resin was then treated with a solution of Fmoc-4-amino-hept-2(trans)-enedioic acid-1-ethyl ester^{1a,b} (2.37 mmol, 1.00 g), DIEA (4.74 mmol, 0.82 ml), and HATU (2.37 mmol, 0.90 g) in DMF (25 ml). The resulting mixture was agitated for 1 h, then washed with DMF (3x10 ml). The Fmoc was then removed by treatment with a solution of 20%
- 30

- 96 -

piperidine-DMF (25 ml), and agitation for 10 min. The resulting resin was washed with DMF (3x10 ml), MeOH (3x10 ml), and CH₂Cl₂ (3x10 ml). (The resin at this stage will be hereafter referred to as Gln-resin) The Gln-resin was then treated with a solution of Fmoc-phenylalanine (4.74 mmol, 1.84 g), DIEA (9.48 mmol, 1.65 ml), and HATU (4.74 mmol, 1.80 g) in DMF (25 ml). The resulting mixture was agitated for 1 h, then washed with DMF (3x25 ml). The Fmoc was removed by treatment with a solution of 20% piperidine-DMF (25 ml), then agitation for 10 min. The resin was washed with DMF (3x10 ml), MeOH (3x10 ml), and CH₂Cl₂ (3x10 ml). The resin was then dried in a vacuum desiccator. (The resin at this stage will be hereafter referred to as Phe-Gln-resin).

EXAMPLE 2

6-Carbamoyl-4S-{2S-[(5-naphthalen-1-yl-1H-pyrrole-2-carbonyl)-amino-3-phenyl-propionylamino]-hex-2(trans)-enoic acid ethyl ester. (Compound 3)



5-Naphthalen-1-yl-1H-pyrrole-2-carboxylic acid chloride

Method 4 General Experimental: Pyrrole-2-carboxylic acid (90.0 mmol, 10.0 g) in diethyl ether (200 ml) was treated with diazomethane (270 mmol, generated from N-nitroso-N-methyl urea), then back titrated with acetic acid until the yellow color dissipated. The solution was washed with saturated aqueous sodium bicarbonate (3x20 ml) and brine (3x20 ml), then concentrated under reduced pressure to provide 10 g (88%) of pyrrole-2-carboxylic acid methyl ester. ¹H NMR (CDCl₃) δ 9.14 (1H, s), 6.98-6.65 (1H, m), 6.94-6.91 (1H, m), 6.29-6.26 (1H, m), 3.86 (3H, s).

A solution of pyrrole-2-carboxylic acid methyl ester (79.9 mmol, 10.0 g) in carbon tetrachloride (300 ml) was heated to 70 °C, then treated dropwise with a solution of bromine (99.9 mmol, 126.0 ml) in carbon tetrachloride (200 ml). The reaction was initiated by the addition of iodine (40 mg). After the addition was

- 97 -

complete, the reaction was held at 70 °C for 10 min, then cooled to room temperature using an ice bath. The mixture was washed with 10% aqueous sodium carbonate (100 ml), followed by water (100 ml). The organics were concentrated under reduced pressure and the residue was purified by silica gel chromatography to provide 4.5 g (27%) of 5-bromo-1H-pyrrole-2-carboxylic acid methyl ester. ¹H NMR (CDCl₃) δ 9.29 (1H, s), 6.80 (1H, dd, J = 3.9, 2.7), 6.23 (1H, dd, J = 3.8, 2.6), 3.88 (3H, s).

Argon gas was bubbled 15 min through a solution of 5-bromo-1H-pyrrole-2-carboxylic acid methyl ester (10.0 mmol, 2.04 g), 1-naphthylboronic acid (30.0 mmol, 5.16 g), 2M aqueous sodium carbonate (20 ml), and DMF (150 ml). The mixture was then treated with tris(dibenzylidienacetone)dipalladium (0) (0.50 mmol, 0.46 g), and triphenylarsine (2.0 mmol, 0.61 g), then heated to reflux under argon for 12 h. The mixture was partitioned between ethyl acetate (500 ml) and water (150 ml). The organics were filtered through celite, washed with brine (3x50 ml), then concentrated under reduced pressure and the residue was purified by silica gel chromatography to provide 2.05 g (81%) of 5-naphthalen-1-yl-1H-pyrrole-2-carboxylic acid methyl ester. ¹H NMR (CDCl₃) δ 9.37 (1H, s), 8.22-8.17 (1H, m), 8.16-7.89 (2H, m), 7.59-7.50 (4H, m), 7.88 (1H, dd, J = 3.9, 2.7), 6.22 (1H, dd, J = 3.8, 2.6), 3.88 (3H, s).

5-Naphthalen-1-yl-1H-pyrrole-2-carboxylic acid methyl ester was diluted with 1:1 dioxane-water (30 ml), and treated with lithium hydroxide hydrate (24.4 mmol, 1.02 g), then heated to reflux for 15 min. The solution was acidified with 20% aqueous citric acid (30 ml), then extracted with ethyl acetate (75 ml). The organics were washed with brine (2x20 ml), then concentrated under reduced pressure. The residue was diluted with CH₂Cl₂ (30 ml), and treated with oxalyl chloride (24.0 mmol, 2.10 ml), and DMF (one drop), then heated to reflux for 30 min. The solution was concentrated under reduced pressure to provide 1.95 g of 5-naphthalen-1-yl-1H-pyrrole-2-carboxylic acid chloride.

Method 1 General Experimental: 5-Naphthalen-1-yl-1H-pyrrole-2-carboxylic acid chloride (0.75 mmol, 0.19 g, prepared as described above) in CH₂Cl₂ (10 ml) and collidine (3.75 mmol, 0.50 ml) was added to Phe-Gln-resin, prepared as described in Example 1, (0.38 mmol, 0.51 g), and agitated for 1 h. The resin was then washed with CH₂Cl₂ (3x10 ml), then suspended in a solution of 95:5 TFA-CH₂Cl₂ (10 ml) and

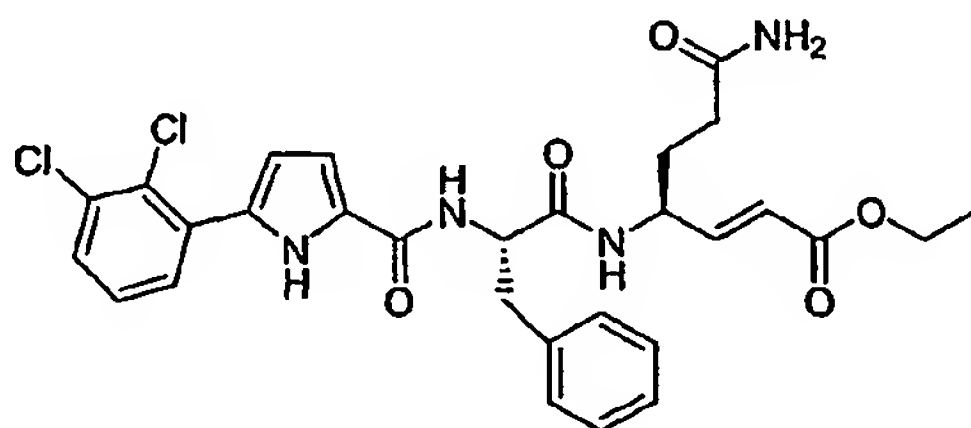
- 98 -

stirred vigorously. The resin was separated by filtration, and the filtrate was concentrated under reduced pressure. The resulting oil was purified by preparative reverse phase chromatography (H₂O-CH₃CN gradient) to provide 21 mg (10 %) of the title product. ¹H NMR (CDCl₃) δ 10.55 (1H, br s), 8.16-8.08 (1H, m), 7.83-7.73 (2H, m), 7.48-7.36 (4H, m), 7.27-7.11 (5H, m), 6.88 (1H, dd, J = 3.7, 2.5), 6.54 (1H, dd, J = 15.7, 5.4), 6.41 (1H, dd, J = 3.7, 2.5), 5.46 (1H, dd, J = 15.7, 1.6), 4.62 (1H, t, J = 7.2), 4.45-4.35 (1H, m), 4.09 (2H, q, J = 7.2), 3.05-2.99 (2H, m), 2.19-2.11 (2H, m), 1.92-1.80 (1H, m), 1.68-1.54 (1H, m), 1.21 (3H, t, J = 7.2). HRMS (FAB) 589.2427 (MNa⁺, calcd. 589.2447).

10

EXAMPLE 3

6-Carbamoyl-4S-(2S-{[5-(2,3-dichloro-phenyl)-1H-pyrrole-2-carbonyl]-amino}-3-phenyl-propionylamino-hex-2(trans)-enoic acid ethyl ester. (Compound 1)



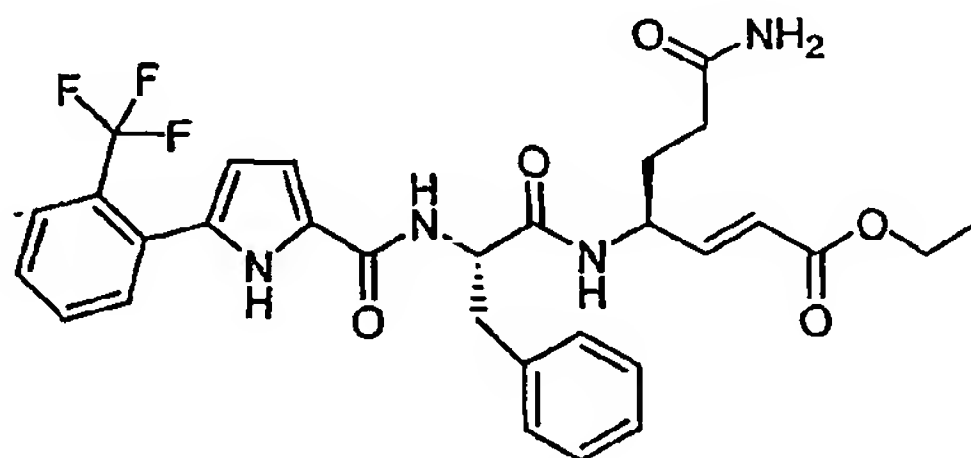
15

5-(2,3-Dichloro-phenyl)-1H-pyrrole-2-carboxylic acid chloride was prepared according to the procedure described in Method 4 of Example 2, starting with 2,3-dichlorophenyl boronic acid. This material was coupled to Phe-Gln resin and converted to the title compound according to the procedure described in Method 1 of Example 2. ¹H NMR (CD₃OD) δ 7.52-7.44 (2H, m), 7.36-7.16 (6H, m), 6.83 (1H, d, J = 3.9), 6.64 (1H, dd, J = 15.8, 5.7), 6.54 (1H, d, J = 3.9), 5.57 (1H, d, J = 6.0), 4.68 (1H, t, J = 7.7), 4.53-4.42 (1H, m), 4.17 (2H, q, J = 7.1), 3.19-3.03 (2H, m), 2.28 (2H, t, J = 7.9), 1.99-1.85 (1H, m), 1.78-1.65 (1H, m), 1.28 (3H, t, J = 7.1). HRMS (MALDI) 607.1501 (MNa⁺, calcd. 607.1491).

20

EXAMPLE 4

6-Carbamoyl-4S-{3-phenyl-2S-[(5-(2-trifluoromethyl-phenyl)-1H-pyrrole-2-carbonyl)-amino]-propionylamino}-hex-2(trans)-enoic acid ethyl ester. (Compound 2)



5

5-(2-Trifluoromethyl-phenyl)-1H-pyrrole-2-carboxylic acid chloride.

Method 6 General Experimental: Magnesium (230.0 mmol, 5.6 g) in THF (200 ml), under an argon atmosphere, was treated with 2-(2-bromoethyl)-1,3-dioxolane (200.0 mmol, 23.5 ml), slowly, keeping the internal temperature below 35 °C with the aid of an ice bath. After completion of the addition, the mixture was held at room temperature for an additional 1 h. 2-Trifluoromethyl benzaldehyde (100 mmol, 13.2 ml) in THF (100 ml) was cooled to -78 °C under an argon atmosphere, then treated with the freshly formed Grignard reagent prepared above. After completion of the addition, the solution was allowed to warm to room temperature, then held at room temperature overnight. The reaction mixture was then poured into saturated aqueous NH₄Cl (200 ml), and extracted with ethyl acetate (2x150 ml). The combined organics were washed with brine (2x75 ml), then concentrated under reduced pressure to give 32.8 g of 3-[1,3]dioxolan-2-yl-1-(2-trifluoromethyl-phenyl)-propan-1-ol, which may be used without further purification. ¹H NMR (CDCl₃) δ 7.78 (1H, d, J = 7.7), 7.62-7.52 (2H, m), 7.34 (1H, t, J = 7.6), 4.92 (1H, t, J = 4.0), 4.00-3.81 (5H, m), 1.90-1.80 (4H, m).

Oxalyl chloride (115.0 mmol, 10.0 ml) in CH₂Cl₂ (200 ml) was cooled to -78 °C under an argon atmosphere. DMSO (240.0 mmol, 17.0 ml) was then added slowly, keeping the internal temperature below -50 °C. After completing the addition, the solution was held 20 minutes at -78 °C. 3-[1,3]Dioxolan-2-yl-1-(2-trifluoromethyl-phenyl)-propan-1-ol (32.8 g of crude material prepared above) in CH₂Cl₂ (30 ml) was added slowly, keeping the internal temperature below -50 °C. The mixture was held at -78 °C for 30 minutes, then treated with Et₃N (480 mmol, 70.0 ml). The mixture was

- 100 -

allowed to warm to room temperature, then washed with water (2x75 ml), then concentrated under reduced pressure to give crude 3-[1,3]dioxolan-2-yl-1-(2-trifluoromethyl-phenyl)-propan-1-one, which may be used without further purification. ¹H NMR (CDCl₃) δ 7.00 (1H, d, J = 7.7), 7.63-7.50 (2H, m), 7.44 (1H, d, J = 7.4), 4.99 (1H, t, J = 4.3), 3.97-3.82 (4H, m), 2.98 (2H, t, J = 7.3) 2.12 (2H, dt, J = 7.4, 4.3).

The crude product 3-[1,3]dioxolan-2-yl-1-(2-trifluoromethyl-phenyl)-propan-1-one, in its entirety, was treated with 1:1 2N HCl : dioxane (150 ml), then heated to reflux for 20 minutes. The resulting mixture was extracted with ethyl acetate (2x150 ml). The combined organics were washed with brine (2x75 ml), then concentrated under reduced pressure to give crude 4-oxo-4-(2-trifluoromethyl-phenyl)-butyrylaldehyde, which may be used without further purification. ¹H NMR (CDCl₃) δ 9.89 (1H, s), 7.71 (1H, d, J = 7.5), 7.66-7.52 (3H, m), 3.15 (2H, t, J = 6.1), 3.01-2.92 (2H, m).

The above prepared 4-oxo-4-(2-trifluoromethyl-phenyl)-butyrylaldehyde was diluted with ethanol (300 ml), and treated with ammonium acetate (1.00 mol, 53.5 g), then heated to reflux for 1 h. This mixture was diluted with ethyl acetate (500 ml) and washed with brine (2x75 ml). The organics were concentrated under reduced pressure and the residue was purified by silica gel chromatography to provide 7.8 g (37% from 2-trifluoromethyl benzaldehyde) of 2-(2-trifluoromethyl-phenyl)-1H-pyrrole. ¹H NMR (CDCl₃) δ 8.51 (1H, br s), 7.74 (1H, d, J = 7.9), 7.60-7.54 (2H, m), 7.44-7.36 (1H, m), 6.95-6.91 (1H, m), 6.44-6.41 (1H, m), 6.33 (1H, dd, J = 6.0, 2.6).

This material was treated with trichloroacetyl chloride, hydrolyzed with lithium hydroxide, and converted to the corresponding acid chloride using oxalyl chloride, as described in Method 5 of Example 12, to give 5-(2-trifluoromethyl-phenyl)-1H-pyrrole-2-carboxylic acid chloride. ¹H NMR (CDCl₃) δ 9.35 (1H, s), 7.80 (1H, d, J = 7.4), 7.68-7.52 (3H, m), 7.26-7.23 (1H, m), 7.53-7.49 (1H, m).

5-(2-Trifluoromethyl-phenyl)-1H-pyrrole-2-carboxylic acid chloride was coupled to Phe-Gln-resin, and converted to the title compound according to the procedure described in Method 1 of Example 2. ¹H NMR (CDCl₃) δ 10.10 (1H, br s), 7.21 (1H, d, J = 7.8), 7.59-7.40 (3H, m), 7.32-7.16 (5H, m), 6.82-6.76 (1H, m), 6.61 (1H, dd, J = 15.8, 5.2), 6.39-6.33 (1H, m), 5.55 (1H, d, J = 15.7), 4.69 (1H, t, J = 7.2),

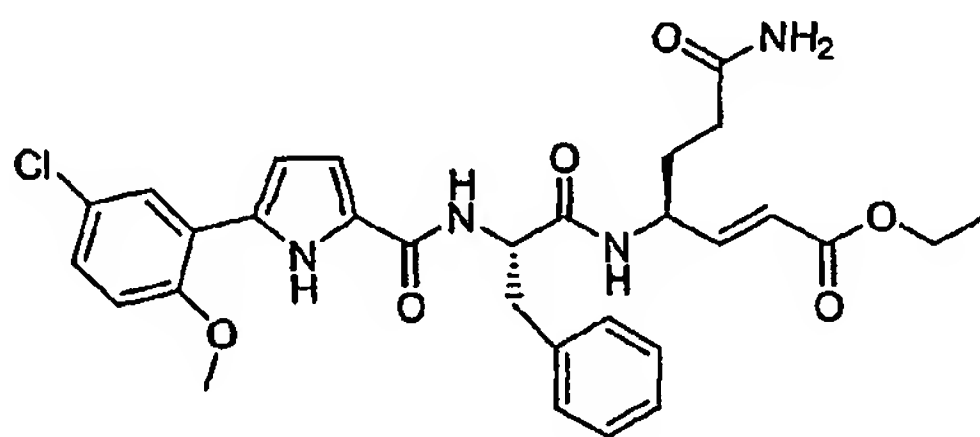
- 101 -

4.54-4.43 (1H, m), 4.16 (2H, q, $J = 7.1$), 3.09 (2H, d, $J = 7.0$), 2.25-2.15 (2H, m), 2.20-1.85 (1H, m), 1.78-1.52 (1H, m), 1.27 (3H, t, $J = 7.1$). HRMS (FAB) 607.2128 (MNa^+ , calcd. 607.2144).

5

EXAMPLE 5

6-Carbamoyl-4S-(2S-[[5-(5-chloro-2-methoxy-phenyl)-1H-pyrrole-2-carbonyl]-amino]-3-phenyl-propionylamino)-hex-2(trans)-enoic acid ethyl ester. (Compound 4)



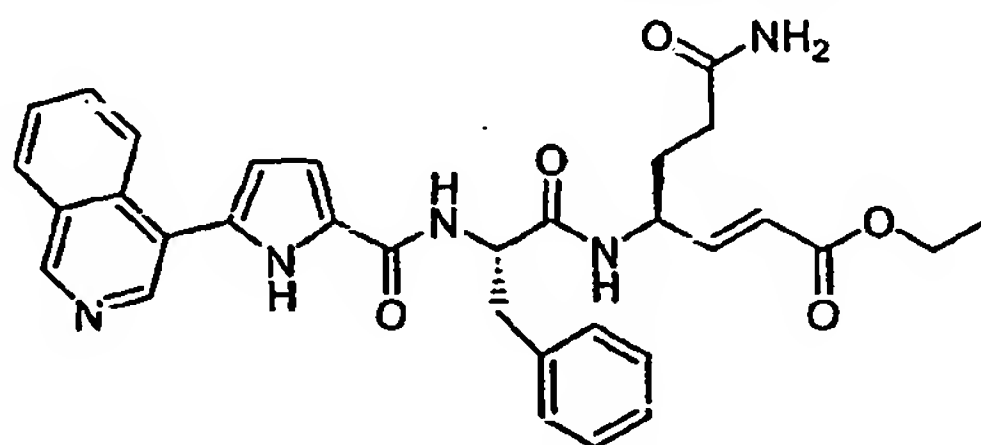
10

5-(5-Chloro-2-methoxy-phenyl)-1H-pyrrole-2-carboxylic acid chloride was prepared according to the procedure described in Method 4 of Example 2, starting with 5-chloro-2-methoxyphenyl boronic acid. This material was coupled to Phe-Gln resin, and converted to the title compound according to the procedure described in Method 1 of Example 2. 1H NMR ($CDCl_3$) δ 10.50 (1H, br s), 7.56 (1H, d, $J = 2.6$), 7.30-7.12 (6H, m), 6.88 (1H, d, $J = 8.9$), 6.79-6.75 (1H, m), 6.60 (1H, dd, $J = 15.7, 5.3$), 6.58-6.55 (1H, m), 5.54 (1H, dd, $J = 15.7, 1.5$), 4.73-4.65 (1H, m), 4.53-4.43 (1H, m), 4.16 (2H, q, $J = 7.1$), 3.93 (3H, s), 3.14-3.04 (2H, m), 2.23-2.15 (2H, m), 1.99-1.84 (1H, m), 1.78-1.62 (1H, m), 1.27 (3H, t, $J = 7.1$). HRMS (FAB) 603.1963 (MNa^+ , calc. 603.1986).

20

EXAMPLE 6

6-Carbamoyl-4S-{2S-[(5-isoquinolin-4-yl-1H-pyrrole-2-carbonyl)-amino]-3-phenyl-propionylamino}-hex-2(trans)-enoic acid ethyl ester. (Compound 5)



25

- 102 -

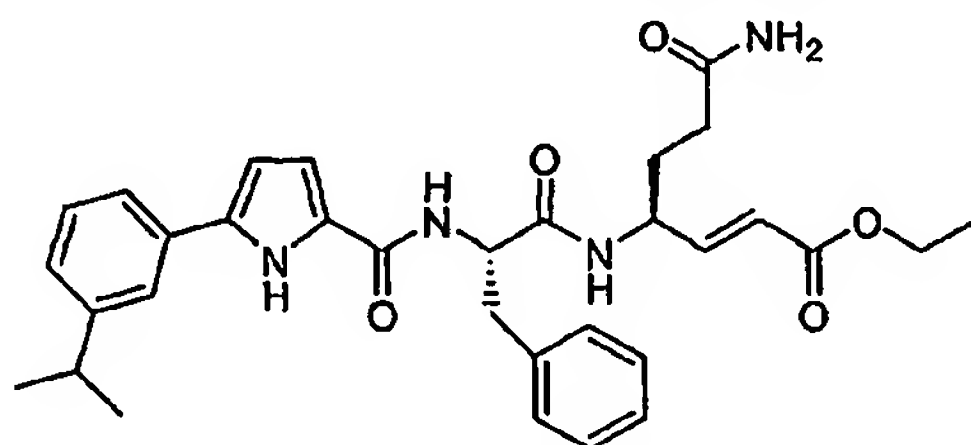
4-Bromoisoquinoline (4.10 mmol, 0.85 g) in toluene (15 ml) was treated with hexamethylditin (5.6 mmol, 2.00 g), and tetrakis(triphenylphosphine)-palladium(0) (0.20 mmol, 0.24 g), then heated to reflux overnight under an argon atmosphere. The resulting mixture was concentrated under reduced pressure, then purified by silica gel chromatography to provide 1.03 g (87%) of 4-(trimethylstannyl)-isoquinoline. ¹H NMR (CDCl₃) δ 9.23 (1H, s), 8.52 (1H, s), 8.00 (1H, d, J = 8.1), 7.78-7.62 (3H, m), 0.5 (9H, s).

5-Bromo-1H-pyrrole-2-carboxylic acid methyl ester (1.49 mmol, 0.30 g, prepared according to the procedure described in Method 4 of Example 2) in NMP (10 ml) was treated with triphenylarsine (0.30 mmol, 91 mg), tris(dibenzylideneacetone) dipalladium(0) (0.07 mmol, 68 mg), and 4-(trimethylstannyl)-isoquinoline (2.22 mmol, 0.65 g), then heated to reflux under an argon atmosphere overnight. The resulting mixture was concentrated under reduced pressure, then purified by silica gel chromatography to provide 0.21 g (55%) of 5-isoquinolin-4-yl-1H-pyrrole-2-carboxylic acid methyl ester. ¹H NMR (CDCl₃) δ 9.81 (1H, br s), 9.35 (1H, s), 8.66 (1H, s), 8.31 (1H, d, J = 8.5), 8.10 (1H, d, J = 8.1), 7.91 (1H, t, J = 15.2), 7.79 (1H, t, J = 15.2), 7.11 (1H, dd, J = 3.8, 2.5), 6.64 (1H, dd, J = 3.7, 2.7), 3.90 (3H, s).

This material was converted to 5-isoquinolin-4-yl-1H-pyrrole-2-carboxylic acid chloride according to the procedures described in Method 4 of Example 2. This material was then coupled to Phe-Gln resin, and converted to the title compound according to the procedure of Method 1 of Example 2. ¹H NMR (CD₃OD) δ 9.20 (1H, br s), 8.51 (1H, s), 8.27 (1H, d, J = 8.6), 8.17 (1H, d, J = 8.1), 7.85 (1H, t, J = 8.4), 7.74 (1H, t, J = 8.2), 7.30-7.17 (9H, m), 7.07 (1H, d, J = 3.8), 6.65 (1H, dd, J = 15.8, 5.6), 6.56 (1H, d, J = 3.8), 5.58 (1H, d, J = 15.8), 4.55-4.46 (1H, m), 4.18 (2H, q, J = 7.1), 3.17 (2H, t, J = 7.8), 2.29 (2H, q, J = 7.9), 2.24-1.68 (4H, m), 1.31 (3H, t, J = 7.1). HRMS (FAB) 590.2363 (MNa⁺, calcd. 590.2379).

EXAMPLE 7

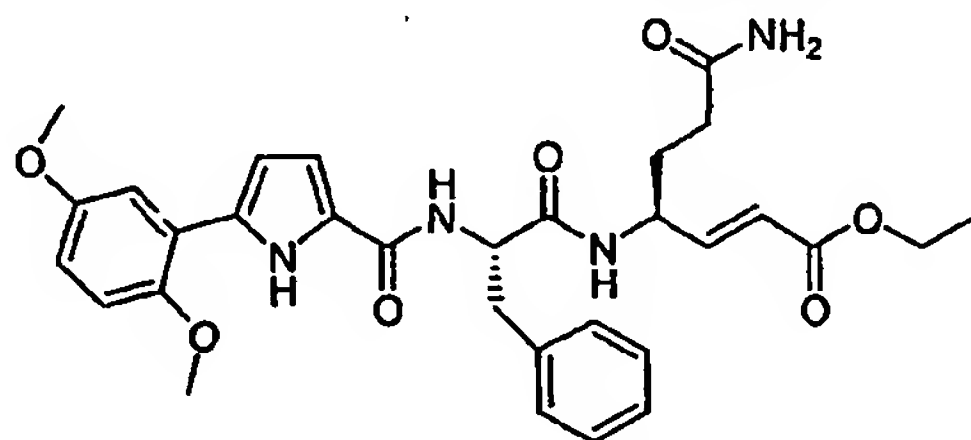
6-Carbamoyl-4S-(2S-[[5-(3-isopropyl-phenyl)-1H-pyrrole-2-carbonyl]-amino]-3-phenyl-propionylamino)-hex-2(trans)-enoic acid ethyl ester. (Compound 6)



5-(3-iso-Propyl-phenyl)-1H-pyrrole-2-carboxylic acid chloride was prepared according to the procedure described in Method 4 of Example 2, starting with 3-isopropylphenyl boronic acid. This product was coupled to Phe-Gln resin, according to the procedure described in Method 1 of Example 2. ¹H NMR (CD₃OD) δ 11.13 (1H, br s), 7.53 (1H, s), 7.47 (1H, d, J = 7.9), 7.32-7.26 (5H, m), 7.25-7.18 (1H, m), 7.14 (1H, d, J = 7.8), 6.93 (1H, dd, J = 3.7, 2.3), 6.65 (1H, dd, J = 15.7, 5.6), 6.53 (1H, dd, J = 3.8, 2.4), 5.58 (1H, dd, J = 15.7, 1.5), 4.71 (1H, t, J = 7.7), 4.53-4.44 (1H, m), 4.18 (2H, q, J = 7.1), 3.20-3.06 (2H, m), 2.94 (1H, d, J = 6.9), 2.30 (2H, t, J = 7.2), 2.00-1.87 (1H, m), 1.80-1.66 (1H, m), 1.29 (3H, t, J = 7.0), 1.28 (6H, d, J = 7.0). HRMS (FAB) 581.2761 (MNa⁺, calcd. 581.2740). Anal. (C₃₂H₃₈N₄O₅ · 0.7 H₂O) C, H, N.

EXAMPLE 8

6-Carbamoyl-4S-(2S-[[5-(2,5-dimethoxy-phenyl)-1H-pyrrole-2-carbonyl]-amino]-3-phenyl-propionylamino)-hex-2-enoic acid ethyl ester. (Compound 7)



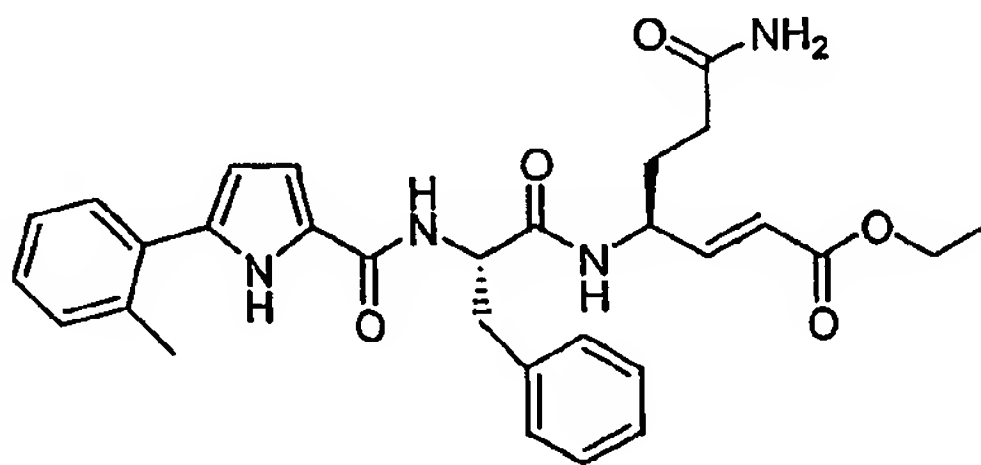
5-(2,5-Dimethoxy-phenyl)-1H-pyrrole-2-carboxylic acid chloride was prepared according to the procedure described in Method 4 of Example 2, starting with 2,5-dimethoxyphenyl boronic acid. This material was coupled to Phe-Gln resin, and

- 104 -

converted to the title compound according to the procedure described in Method 1 of Example 2. ¹H NMR (CDCl₃) δ 10.55 (1H, br s), 7.37-7.20 (7H, m), 6.90 (1H, d, J = 9.0), 6.81 (1H, d, J = 3.0), 6.65 (1H, dd, J = 15.7, 5.3), 6.63-6.57 (1H, m), 5.61 (1H, dd, J = 15.7, 1.5), 4.73-4.65 (1H, m), 4.53-4.43 (1H, m), 4.16 (2H, q, J = 7.1), 3.89 (3H, s), 3.80 (3H, s), 3.14-3.04 (2H, m), 2.35-2.20 (2H, m), 2.10-1.85 (1H, m), 1.80-1.70 (1H, m), 1.27 (3H, t, J = 7.1). HRMS (FAB) 599.2499 (MNa⁺, calcd. 599.2482).

EXAMPLE 9

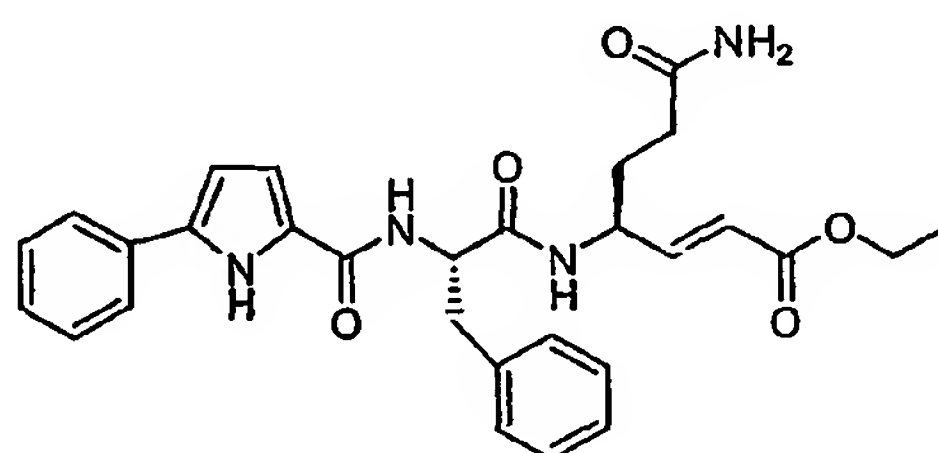
6-Carbamoyl-4S-{3-phenyl-2S-[(5-o-tolyl-1H-pyrrole-2-carbonyl)-amino]-propionylamino}-hex-2(trans)-enoic acid ethyl ester. (Compound 9)



5-(o-Tolyl)-1H-pyrrole-2-carboxylic acid chloride was prepared according to the procedure described in Method 4 of Example 2, starting with o-tolyl boronic acid. This material was coupled to Phe-Gln resin, and converted to the title compound according to the procedure described in Method 1 of Example 2. ¹H NMR (CDCl₃) δ 10.10 (1H, br s), 7.38-7.15 (7H, m), 6.81 (1H, d, J = 7.2), 6.77-6.70 (1H, m), 6.65-6.55 (2H, m), 6.29 (1H, s), 5.58 (1H, d, J = 15.5), 4.76-4.65 (1H, m), 4.58-4.45 (1H, m), 4.18 (2H, q, J = 7.1), 3.20-3.03 (2H, m), 2.20-2.00 (5H, m), 1.93-1.77 (1H, m), 1.72-1.57 (1H, m), 1.90 (3H, t, J = 7.1). HRMS (FAB) 553.2438 (MNa⁺, calcd. 553.2427). Anal. (C₃₀H₃₄N₄O₅ · 1.0 H₂O) C, H, N.

EXAMPLE 10

6-Carbamoyl-4S-{3-phenyl-2S-[(5-phenyl-1H-pyrrole-2-carbonyl)-amino]-propionylamino}-hex-2(trans)-enoic acid ethyl ester. (Compound 10)



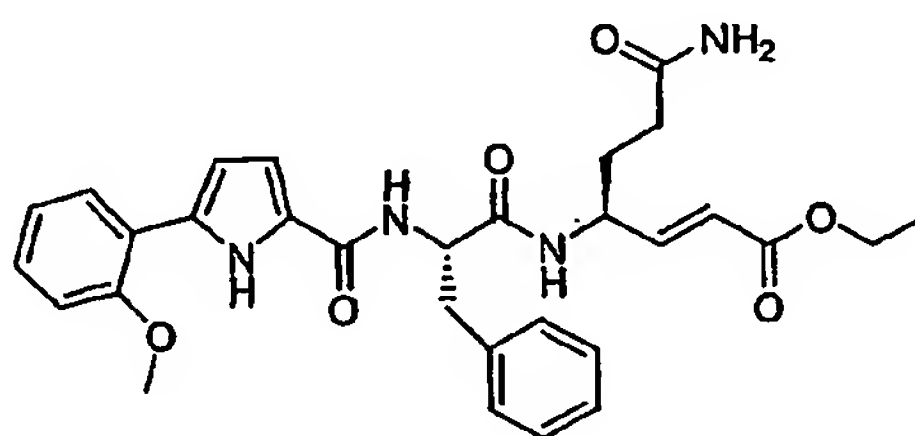
5

5-Phenyl-1H-pyrrole-2-carboxylic acid chloride was prepared according to the procedure described in Method 4 of Example 2, starting with phenyl boronic acid. This material was coupled to Phe-Gln resin, and converted to the title compound according to the procedure described in Method 1 of Example 2. ¹H NMR (CDCl₃) δ 11.15 (1H, br s), 8.27 (1H, d, J=4.8), 7.67 (2H, d, J=7.3), 7.39 (2H, t, J=7.8), 7.33-7.19 (5H, m), 7.76-7.71 (1H, m), 6.66 (1H, dd, J=15.7, 5.7), 6.57-6.53 (1H, m), 5.59 (1H, d, J=15.7), 4.71 (1H, t, J=7.6), 4.55-4.45 (1H, m), 4.19 (2H, q, J=7.2), 3.33 (2H, q, J=8.3), 2.30 (2H, t, J=7.3), 2.03-1.87 (1H, m), 1.80-1.68 (1H, m), 1.21 (3H, t, J=7.1). HRMS (FAB) 539.2283 (MNa⁺, calcd. 539.2270). Anal. (C₂₉H₃₂N₄O₅ · 0.7 H₂O + 0.1 TFA), C, H, N.

15

EXAMPLE 11

6-Carbamoyl-4S-(2S-{[5-(2-methoxy-phenyl)-1H-pyrrole-2-carbonyl]-amino}-3-phenyl-propionylamino)-hex-2(trans)-enoic acid ethyl ester. (Compound 11)



20

25

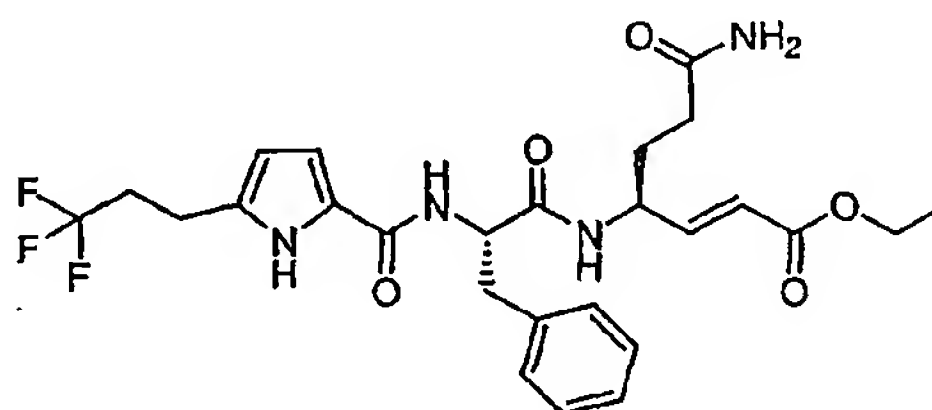
5-(2-Methoxy-phenyl)-1H-pyrrole-2-carboxylic acid chloride was prepared according to the procedure described in Method 4 of Example 2, starting with 2-methoxyphenyl boronic acid. This material was coupled to Phe-Gln resin, and converted to the title compound according to the procedure described in Method 1 of

- 106 -

Example 2. ^1H NMR (CDCl_3) δ 10.73 (1H, s), 8.27 (1H, d, $J = 8.3$), 7.69 (1H, d, $J = 7.6$), 7.33-7.19 (5H, m), 7.10 (1H, d, $J = 8.3$), 7.01 (1H, t, $J = 7.7$), 6.95 (1H, br s), 6.72-6.62 (2H, m), 5.61 (1H, d, $J = 15.8$), 4.72 (1H, t, $J = 7.2$), 4.57-4.46 (1H, m), 4.20 (2H, q, $J = 7.1$), 3.99 (3H, s), 3.22-3.06 (2H, m), 2.32 (2H, t, $J = 7.4$), 2.03-1.88 (1H, m), 1.82-1.70 (1H, m), 1.32 (3H, t, $J = 7.1$). HRMS (MALDI) 569.2398 (MNa^+ , calcd. 569.2376). Anal. ($\text{C}_{30}\text{H}_{34}\text{N}_4\text{O}_6 \cdot 0.9 \text{H}_2\text{O} \cdot 0.4 \text{TFA}$) C, H, N.

EXAMPLE 12

6-Carbamoyl-4S-(3-phenyl-2S-{[5-(3,3,3-trifluoro-propyl)-1H-pyrrole-2-carbonyl]-amino}-propionylamino)-hex-2(trans)-enoic acid ethyl ester. (Compound 22)



5-(3,3,3-Trifluoro-propyl)-1H-pyrrole-2-carboxylic acid chloride

Method 5 General Experimental: 4,4,4-Trifluorobutyric acid (70.0 mmol, 10.0 g) in CH_2Cl_2 (190 ml) was treated with oxalyl chloride (140 mmol, 12.3 ml) and DMF (1 drop), then heated to reflux for 1 h. Solvent and excess oxalyl chloride were removed from the volatile product by simple distillation of the reaction mixture at atmospheric pressure to provide crude 4,4,4-trifluorobutyric acid chloride (6.4 g). ^1H NMR (CDCl_3) δ 3.20 (2H, t, $J = 7.2$), 2.65-2.45 (2H, m).

4,4,4-Trifluorobutyric acid chloride (6.4 g from above) in CH_2Cl_2 (80 ml) was treated with O,N-dimethylhydroxylamine hydrochloride (60.0 mmol, 5.85 g). The mixture was cooled to 0 °C, then treated with pyridine (160.0 mmol, 12.9 ml), then allowed to warm to room temperature overnight. The mixture was diluted with CH_2Cl_2 (200 ml), then washed with brine (2x50 ml). Solvent was removed from the volatile product by simple distillation at atmospheric pressure to provide 20 g of 4,4,4-trifluoro-N-methoxy-N-methyl butyramide, which may be used without further purification. ^1H NMR (CDCl_3) δ 3.70 (3H, s), 3.19 (3H, s), 2.78-2.65 (2H, m), 2.57-2.40 (2H, m).

- 107 -

Mg (92.0 mmol, 2.2 g) in THF (80 ml), under an argon atmosphere, was treated with 2-(2-bromoethyl)-[1,3]dioxolane (80 mmol, 9.4 ml), while keeping the internal temperature below 35 °C with the aid of an ice bath. After the addition was complete, the mixture was stirred for 2 h at room temperature, then cooled to -78 °C. Crude
5 4,4,4-trifluoro-N-methoxy-N-methyl butyramide (20 g, prepared above) in THF (40 ml) was cooled to -78 °C, then the freshly prepared Grignard reagent was transferred via cannula into the amide solution at -78 °C. The resulting mixture was allowed to warm to room temperature, held at room temperature overnight, then poured into saturated aqueous ammonium chloride (200 ml). The mixture was extracted with ethyl acetate
10 (3x75 ml). The combined organics were washed with brine (2x75 ml) and concentrated under reduced pressure to provide crude 1-[1,3]dioxolan-2-yl-6,6,6-trifluoro-hexan-3-one (18 g) ¹H NMR (CDCl₃) δ 4.91 (1H, t, J = 4.1), 3.97-3.82 (4H, m), 2.70 (2H, t, J = 7.3), 2.57 (2H, t, J = 7.2), 2.49-2.34 (2H, m), 2.01 (2H, dt, J = 7.3, 4.1).

Crude 1-[1,3]dioxolan-2-yl-6,6,6-trifluoro-hexan-3-one (18 g, prepared above)
15 in 1:1 2N HCl-dioxane (80 ml) was heated to reflux for 20 minutes, then neutralized with aqueous sodium bicarbonate (100 ml), then extracted with ethyl acetate (3x75 ml). The combined organics were washed with brine (2x50 ml), then concentrated under reduced pressure to provide crude 7,7,7-trifluoro-4-oxo-heptanal (10 g), which may be used without further purification. ¹H NMR (CDCl₃) δ 9.80 (1H, s), 2.85-2.70 (6H, m),
20 2.47-2.35 (2H, m).

Crude 7,7,7-trifluoro-4-oxo-heptanal (10 g, prepared above) in ethanol (100 ml) was treated with ammonium chloride (400 mmol, 21 g), then heated to reflux for 1 h. The resulting solution was diluted with ethyl acetate (300 ml) and washed with brine (2x50 ml). The organics were concentrated under reduced pressure. Purification of the
25 residue by silica gel chromatography provided 1.3 g (21% overall from 4,4,4-trifluorobutyric acid) of 2-(3,3,3-trifluoro-propyl)-1H-pyrrole. ¹H NMR (CDCl₃) δ 7.98 (1H, br s), 6.71 (1H, dd, J = 4.1, 2.6), 6.15 (1H, dd, J = 5.9, 2.8), 5.99-5.94 (1H, m), 2.92-2.85 (2H, m), 2.52-2.35 (2H, m).

2-(3,3,3-Trifluoro-propyl)-1H-pyrrole (8.15 mmol, 1.33 g) was added to a
30 solution of trichloroacetyl chloride (8.15 mmol, 0.91 ml) in diethyl ether (10 ml). The resulting solution was held at room temperature for 1h, then concentrated under

- 108 -

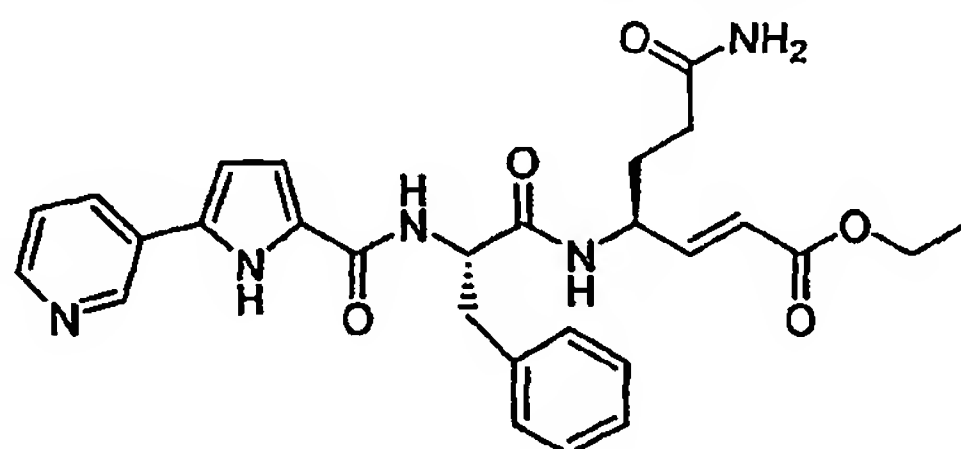
reduced pressure. The resulting solid was dissolved in 1:1 dioxane-water (20 ml), treated with lithium hydroxide (24.5 mmol, 0.59 g), and heated to reflux for 30 minutes. After cooling to room temperature, the solution was acidified with saturated aqueous citric acid (20 ml), then extracted with ethyl acetate (2x50 ml). The combined
5 organics were concentrated under reduced pressure. Purification of the resulting solid by silica gel chromatography provided 1.15 g (68%) of 5-(3,3,3-trifluoropropyl)-1H-pyrrole-2-carboxylic acid. ¹H NMR (CDCl₃) δ 9.33 (1H, br s), 6.99 (1H, dd, J = 3.7, 2.5), 6.07 (1H, t, J = 3.3), 2.96-2.89 (2H, m), 2.55-2.39 (2H, m).

5-(3,3,3-trifluoropropyl)-1H-pyrrole-2-carboxylic acid (5.55 mmol, 1.15 g) in
10 CH₂Cl₂ (10 ml) was treated with oxalyl chloride (16.7 mmol, 1.5 ml), then DMF (1 drop). The solution was heated to reflux for 1 h, then concentrated under reduced pressure to provide 5-(3,3,3-trifluoropropyl)-1H-pyrrole-2-carboxylic acid chloride (1.04 g). ¹H NMR (CDCl₃) δ 10.25 (1H, br s), 7.12 (1H, dd, J = 4.0, 2.6), 6.12 (1H, dd, J = 3.8, 2.7), 3.05-2.88 (2H, m), 2.59-2.41 (2H, m).

15 The 5-(3,3,3-trifluoro-propyl)-1H-pyrrole-2-carboxylic acid chloride was coupled to Phe-Gln resin, and converted to the title compound according to the procedure described in Method 1 of Example 2. ¹H NMR (CDCl₃) δ 10.30 (1H, br s), 7.41 (1H, d, J = 8.5), 7.29-7.13 (4H, m), 6.61 (1H, dd, J = 15.7, 5.3), 6.63 (1H, m), 5.93 (1H, br s), 5.53 (1H, dd, J = 15.7, 1.3), 4.65 (1H, t, J = 7.1), 4.53-4.42 (1H, m), 4.15
20 (2H, q, J = 7.1), 3.05-3.00 (2H, m), 2.88-2.79 (2H, m), 2.45-2.30 (2H, m), 2.20-2.10 (2H, m), 1.86-1.83 (1H, m), 1.75-1.66 (1H, m), 1.27 (3H, t, J = 7.1). HRMS (MALDI) 559.2131 (MNa⁺, calcd. 559.2144).

EXAMPLE 13

25 6-Carbamoyl-4S-{3-phenyl-2S-[(5-pyridin-3-yl-1H-pyrrole-2-carbonyl)-amino]-propionylamino}-hex-2(trans)-enoic acid ethyl ester. (Compound 8)



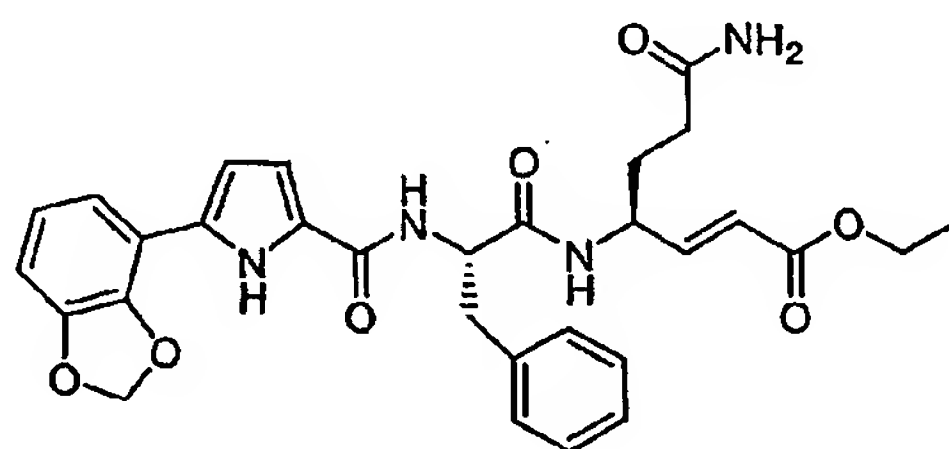
- 109 -

5-Pyridin-3-yl-1H-pyrrole-2-carboxylic acid chloride was prepared according to the procedure described in Method 5 of Example 12, starting with 3-pyridine carboxylic acid. This material was coupled to Phe-Gln resin, and converted to the title compound according to the procedure described in Method 1 of Example 2. ¹H NMR (CD₃OD) δ

8.88 (1H, s), 8.41 (1H, d, J = 3.4), 8.11 (1H, d, J = 7.9), 7.46 (1H, dd, J = 8.0, 4.5),
 7.29-7.19 (5H, m), 6.90 (1H, d, J = 3.9), 6.68 (1H, d, J = 3.9), 6.66 (1H, dd, J = 15.6,
 5.6), 5.59 (1H, d, J = 15.6), 4.71 (1H, t, J = 7.7), 4.51-4.48 (1H, m), 4.19 (2H, q, J =
 7.1), 3.11 (2H, t, J = 8.5), 2.25-2.10 (2H, m), 1.96-1.82 (1H, m), 1.75-1.60 (1H, m),
 1.28 (3H, t, J = 7.1). HRMS (MALDI) 540.2217 (MNa⁺, calcd. 540.2223).

EXAMPLE 14

4S-{2S-[(5-Benzo{1,3}dioxol-4-yl-1H-pyrrole-2-carbonyl)-amino-3-phenyl-propionylamino]-6-carbamoyl-hex-2(trans)-enoic acid ethyl ester. (Compound 12)

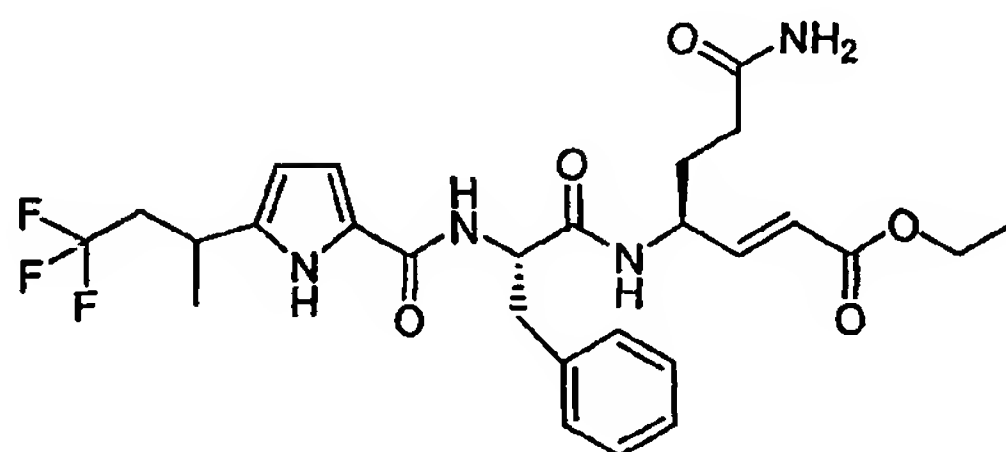


5-Benzo[1,3]dioxol-4-yl-1H-pyrrole-2-carboxylic acid chloride was prepared according to the procedure described in Method 5 of Example 12, starting with benzo[1,3]dioxole-4-carboxylic acid. This material was coupled to Phe-Gln resin, and converted to the title compound according to the procedure described in Method 1 of Example 2. ¹H NMR (CD₃OD) δ 7.32-7.24 (5H, m), 7.18 (1H, dd, J = 7.1, 1.1), 6.95 (1H, d, J = 3.9), 6.89 (1H, t, J = 5.1), 6.75 (1H, dd, J = 7.7, 1.1), 6.70-6.63 (2H, m), 6.08 (2H, s), 5.58 (1H, d, J = 15.3), 4.70 (1H, t, J = 7.7), 4.55-4.42 (1H, m), 4.18 (2H, q, J = 7.2), 3.10 (2H, t, J = 8.0), 2.31 (2H, t, J = 8.5), 1.96-1.82 (1H, m), 1.75-1.60 (1H, m), 1.27 (3H, t, J = 7.1). HRMS (FAB) 583.2148 (MNa⁺, calcd. 583.2169).

- 110 -

EXAMPLE 15

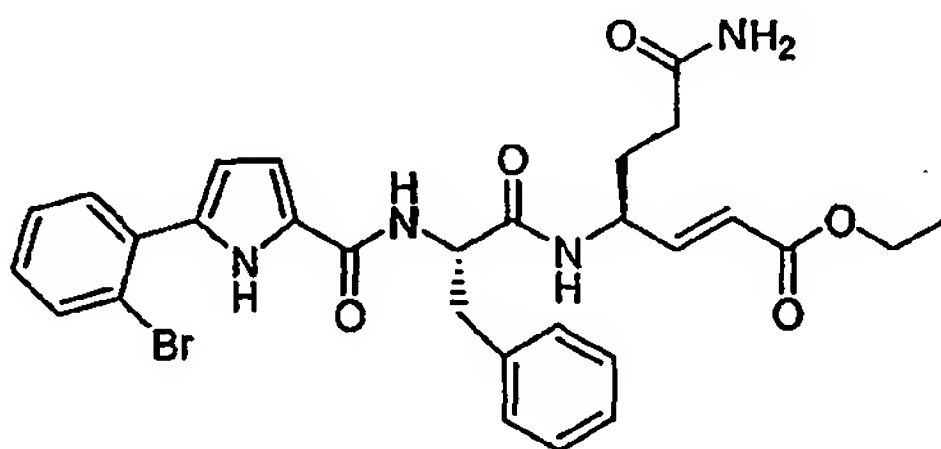
6-Carbamoyl-4S-(3-phenyl-2S-{{[5-(3,3,3-trifluoro-1-methyl-propyl)-1H-pyrrole-2-carbonyl]-amino}-propionylamino)-hex-2(trans)-enoic acid ethyl ester. (Compound 13)



5
 5-(3,3,3-trifluoro-1-methyl-propyl)-1H-pyrrole-2-carboxylic acid chloride was prepared according to the procedure described in Method 5 of Example 12, starting with 4,4,4-trifluoro-2-methyl butyric acid. This material was coupled to Phe-Gln resin, and converted to the title compound according to the procedure described in Method 1
 10 of Example 2. ^1H NMR (CDCl_3) δ 10.00 (1H, br s), 7.32-7.16 (5H, m), 6.99 (1H, d, J = 6.9), 6.77 (1H, br s), 6.67 (1H, dd, J = 15.7, 5.4), 6.62-6.58 (1H, m), 6.20-6.01 (2H, m), 5.97 (1H, t, J = 3.0), 5.66 (1H, d, J = 15.9), 4.86-4.75 (1H, m), 4.60-4.48 (1H, m), 4.17 (2H, q, J = 7.1), 3.23-3.04 (3H, m), 2.52-2.38 (1H, m), 2.22-2.12 (3H, m), 1.83-1.70 (1H, m), 1.23 (3H, d, J = 7.0), 1.30 (3H, t, J = 7.2). HRMS (MALDI) 573.2295 (MNa^+ ,
 15 calcd. 573.2301). Anal. ($\text{C}_{27}\text{H}_{33}\text{N}_4\text{O}_5\text{F}_3 \cdot 0.1 \text{ TFA}$) C, H, N.

EXAMPLE 16

4S-(2S-{{[5-(2-Bromo-phenyl)-1H-pyrrole-2-carbonyl]-amino}-3-phenyl-propionylamino)-6-carbamoyl-hex-2(trans)-enoic acid ethyl ester. (Compound 14)



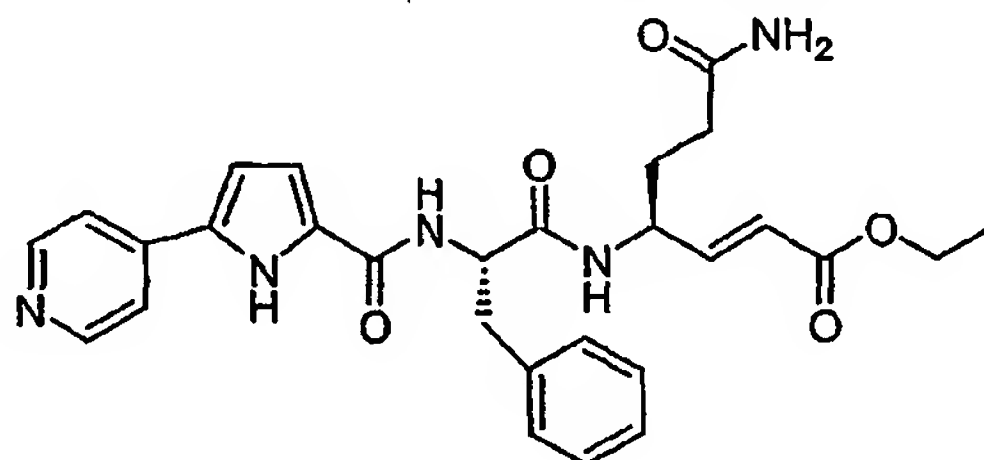
20
 5-(2-bromo-phenyl)-1H-pyrrole-2-carboxylic acid chloride was prepared according to the procedure described in Method 5 of Example 12, starting with 2-bromobenzoic acid. This material was coupled to Phe-Gln resin, and converted to the
 25 title compound according to the procedure described in Method 1 of Example 2. ^1H

- 111 -

NMR (CDCl₃) δ 10.30 (1H, br s), 7.56 (1H, d, J = 7.9), 7.41 (1H, dd, J = 7.7, 1.5), 7.31-7.13 (7H, m), 7.08 (1H, dt, J = 7.8, 1.2), 7.01 (1H, d, J = 8.6), 6.80-6.74 (1H, m), 6.64 (1H, dd, J = 15.7, 5.3), 6.54-6.49 (1H, m), 6.26 (1H, br s), 6.14 (1H, br s), 5.63 (1H, dd, J = 15.7, 1.2), 4.83-4.72 (1H, m), 4.58-4.46 (1H, m), 4.37 (2H, q, J = 7.1), 3.20-3.02 (2H, m), 2.25-2.10 (2H, m), 1.96-1.82 (1H, m), 1.75-1.60 (1H, m), 1.29 (3H, t, J = 7.1). HRMS (MALDI) 617.1365 (MNa⁺, calcd. 617.1376). Anal. (C₂₉H₃₁N₄O₅Br · 0.2 H₂O · 0.3 TFA) C, H, N.

EXAMPLE 17

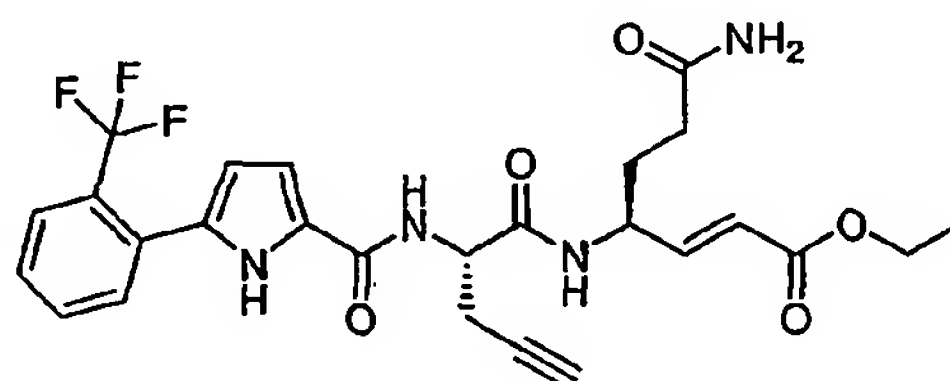
6-Carbamoyl-4S-{3-phenyl-2S-[(5-pyridin-4-yl-1H-pyrrole-2-carbonyl)-amino]-propionylamino}-hex-2(trans)-enoic acid ethyl ester. (Compound 15)



5-Pyridin-4-yl-1H-pyrrole-2-carboxylic acid chloride was prepared according to the procedure described in Method 5 of Example 12, starting with 4-pyridine carboxylic acid. This material was coupled to Phe-Gln resin, and converted to the title compound according to the procedure described in Method 1 of Example 2. ¹H NMR (CD₃OD) δ 8.50 (2H, d, J = 6.7), 7.70 (2H, d, J = 6.4), 7.30-7.19 (5H, m), 6.97 (1H, d, J = 3.9), 6.84 (1H, d, J = 4.0), 6.66 (1H, dd, J = 15.8, 5.6), 5.59 (1H, d, J = 15.7), 4.72 (1H, t, J = 15.4), 4.60-4.40 (1H, m), 4.18 (2H, q, J = 7.1), 3.17 (2H, t, J = 7.9), 2.25-2.10 (2H, m), 1.96-1.82 (1H, m), 1.75-1.60 (1H, m), 1.28 (3H, t, J = 7.1). HRMS (MALDI) 540.2217 (MNa⁺, calcd. 540.2223).

EXAMPLE 18

6-Carbamoyl-4S-(2S-{{[5-(2-trifluoromethyl-phenyl)-1H-pyrrole-2-carbonyl]-amino}-pent-4-ynoylamino)-hex-2(trans)-enoic acid ethyl ester. (Compound 16)

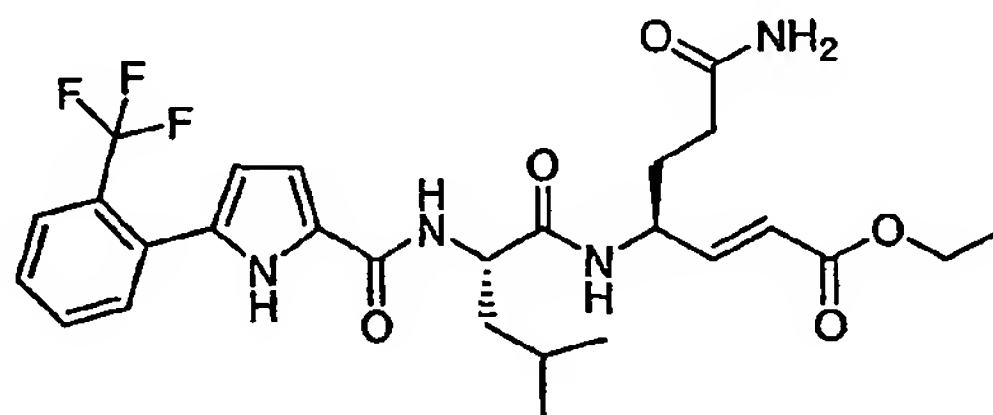


5
Gln-resin was coupled with Fmoc-propargyl glycine, deprotected, then coupled to 5-(2-trifluoromethyl-phenyl)-1H-pyrrole-2-carboxylic acid chloride (prepared according to the procedure described in Method 6 of Example 4), following Method 1 of Example 2. ¹H NMR (CDCl₃) δ 10.13 (1H, s), 7.73 (1H, d, J = 7.8), 7.60-7.40 (4H, m), 7.15 (1H, d, J = 7.6), 6.90-6.75 (2H, m), 6.38 (1H, s), 6.15 (2H, br s), 6.02 (1H, d, J = 16.3), 4.78-4.68 (1H, m), 4.68-4.55 (1H, m), 4.15 (2H, q, J = 7.1), 2.80-2.20 (4H, m), 2.12 (1H, s), 2.08-1.90 (1H, m), 1.90-1.75 (1H, m), 1.25 (3H, t, J = 7.1). HRMS (MALDI) 555.1828 (MNa⁺, calcd. 555.1831). Anal. (C₂₆H₂₇F₃N₄O₅ • 0.8 H₂O).

10

EXAMPLE 19

6-Carbamoyl-4S-(4-methyl-2S-{{[5-(2-trifluoromethyl-phenyl)-1H-pyrrole-2-carbonyl]-amino}-pentanoylamino)-hex-2(trans)-enoic acid ethyl ester. (Compound 17)



20
Gln-resin was coupled with Fmoc-leucine, deprotected, then coupled to 5-(2-trifluoromethyl-phenyl)-1H-pyrrole-2-carboxylic acid chloride (prepared according to the procedure described in Method 6 of Example 4), following Method 1 of Example 2. ¹H NMR (CDCl₃) δ 10.06 (1H, s), 7.70 (1H, d, J = 7.6), 7.60-7.38 (4H, m), 7.13 (1H, d, J = 7.8), 6.38-6.75 (2H, m), 6.36 (2H, br s), 6.19 (1H, br s), 5.91 (1H, d, J = 15.5), 4.72-4.60 (1H, m), 4.60-4.45 (1H, m), 4.17 (2H, q, J = 7.1), 2.28-2.15 (2H, m), 2.00-1.85 (1H, m), 1.80-1.60 (4H, m), 1.27 (3H, t, J = 7.1), 0.92 (3H, d, J = 5.5), 0.88 (3H, d, J =

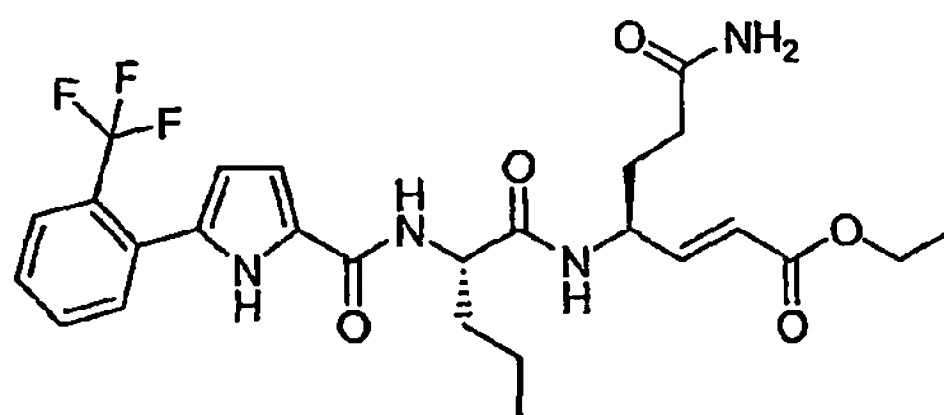
25

- 113 -

5.5). HRMS (MALDI) 573.2292 (MNa^+ , calcd. 573.2301). Anal. ($\text{C}_{27}\text{H}_{33}\text{N}_4\text{F}_3\text{O}_5 \cdot 0.2 \text{H}_2\text{O} \cdot 0.2 \text{TFA}$) C, H, N.

EXAMPLE 20

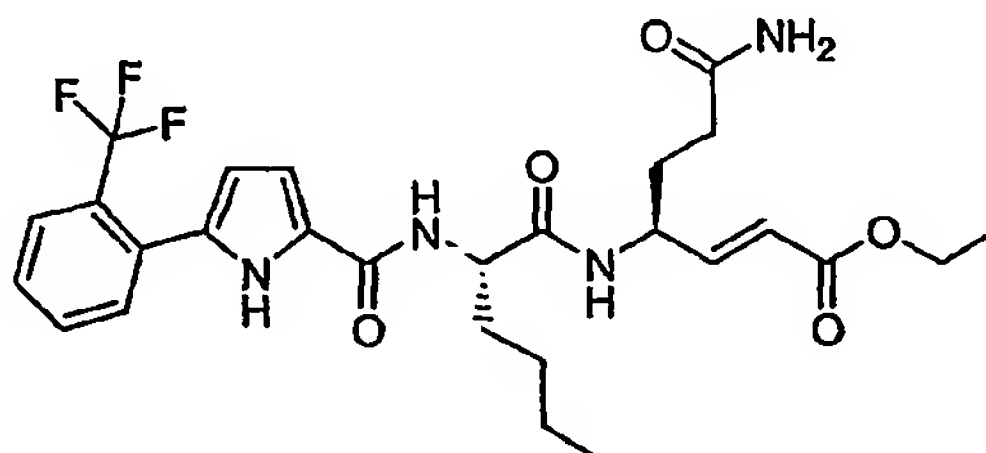
5 6-Carbamoyl-4S-(2S-{{[5-(2-trifluoromethyl-phenyl)-1H-pyrrole-2-carbonyl]-amino}-pentanoylamino)-hex-2(trans)-enoic acid ethyl ester. (Compound 18)



Gln-resin was coupled with Fmoc-norvaline, deprotected, then coupled to 5-(2-
 10 trifluoromethyl-phenyl)-1H-pyrrole-2-carboxylic acid chloride (prepared according to the procedure described in Method 6 of Example 4), following Method 1 of Example 2. ^1H NMR (CDCl_3) δ 10.21 (1H, s), 7.69 (1H, d, $J = 7.7$), 7.64 (1H, d, $J = 8.0$), 7.55-7.33 (4H, m), 6.88-6.75 (2H, m), 6.45-6.20 (3H, m), 5.91 (1H, d, $J = 15.7$), 4.65-4.50 (2H, m), 4.15 (2H, q, $J = 7.1$), 2.25-2.15 (2H, m), 2.00-1.60 (4H, m), 1.48-1.28 (2H, m), 1.25
 15 (3H, t, $J = 7.1$), 0.89 (3H, t, $J = 7.2$). HRMS (MALDI) 559.2158 (MNa^+ , calcd. 559.2144).

EXAMPLE 21

6-Carbamoyl-4S-(2S-{{[5-(2-trifluoromethyl-phenyl)-1H-pyrrole-2-carbonyl]-amino}-
 20 hexanoylamino)-hex-2(trans)-enoic acid ethyl ester. (Compound 19)



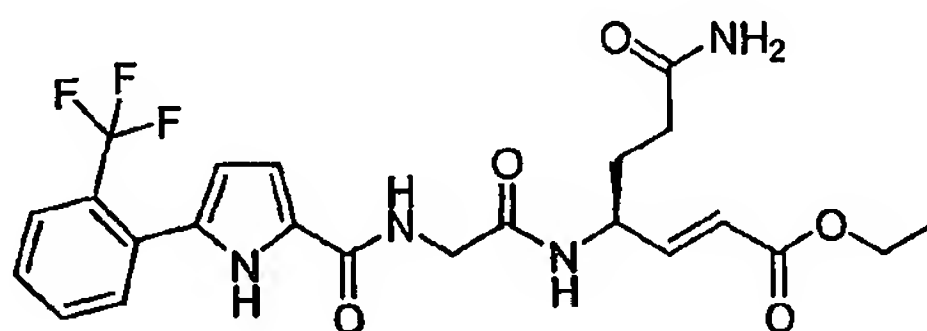
Gln-resin was coupled with Fmoc-norleucine, deprotected, then coupled to 5-(2-
 25 trifluoromethyl-phenyl)-1H-pyrrole-2-carboxylic acid chloride (prepared according to the procedure described in Method 6 of Example 4), following Method 1 of Example 2.

- 114 -

¹H NMR (CDCl₃) δ 10.08 (1H, br s), 7.71 (1H, d, J = 7.7), 7.56-7.38 (4H, m), 7.09 (1H, d, J = 7.9), 6.88-6.76 (2H, m), 6.37 (1H, s), 6.32 (1H, br s), 6.18 (1H, br s), 5.92 (1H, d, J = 15.0), 4.64-4.52 (2H, m), 4.16 (2H, q, J = 7.1), 2.30-2.15 (2H, m), 2.00-1.65 (4H, m), 1.40-1.22 (7H, m), 0.87 (3H, t, J = 6.3). HRMS (MALDI) 573.2307 (MNa⁺, calcd. 573.2301).

EXAMPLE 22

6-Carbamoyl-4S-(2S-{{5-(2-trifluoromethyl-phenyl)-1H-pyrrole-2-carbonyl]-amino}-acetylamino)-hex-2(trans)-enoic acid ethyl ester. (Compound 20)

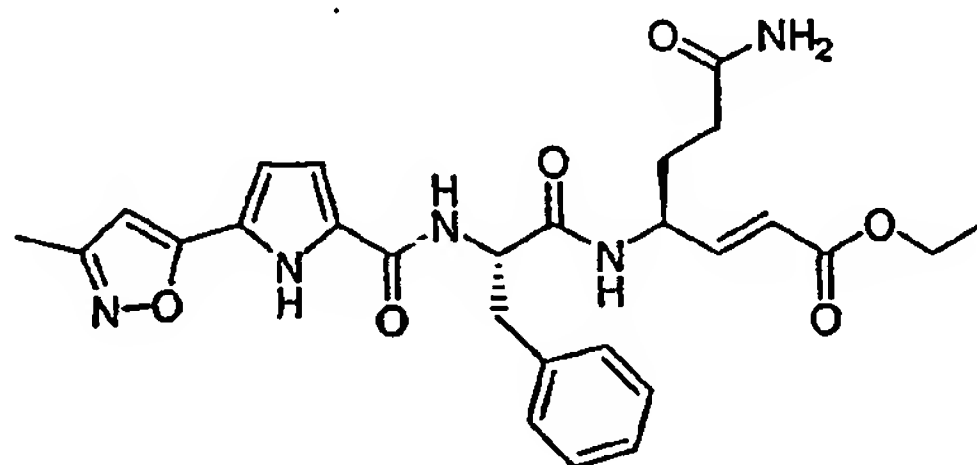


Gln-resin was coupled with Fmoc-glycine, deprotected, then coupled to 5-(2-trifluoromethyl-phenyl)-1H-pyrrole-2-carboxylic acid chloride (prepared according to the procedure described in Method 6 of Example 4), following Method 1 of Example 2.

¹H NMR (CD₃OD) δ 11.18 (1H, s), 7.79 (1H, d, J = 7.8), 7.70-7.50 (3H, m), 6.92-6.88 (1H, m), 6.85 (1H, d, J = 5.5), 6.32 (1H, m), 5.97 (1H, dd, J = 15.7, 1.7), 4.64-4.54 (1H, m), 4.17 (2H, q, J = 7.1), 4.02 (2H, d, J = 2.4), 2.35-2.27 (2H, m), 2.06-1.94 (1H, m), 1.90-1.75 (1H, m), 1.27 (3H, t, J = 7.1). HRMS (MALDI) 495.1874 (MNa⁺, calcd. 495.1855).

EXAMPLE 23

6-Carbamoyl-4S-(2S-{{5-(3-methyl-isoxazol-5-yl)-1H-pyrrole-2-carbonyl]-amino}-3-phenyl-propionylamino)-hex-2(trans)-enoic acid ethyl ester. (Compound 21)



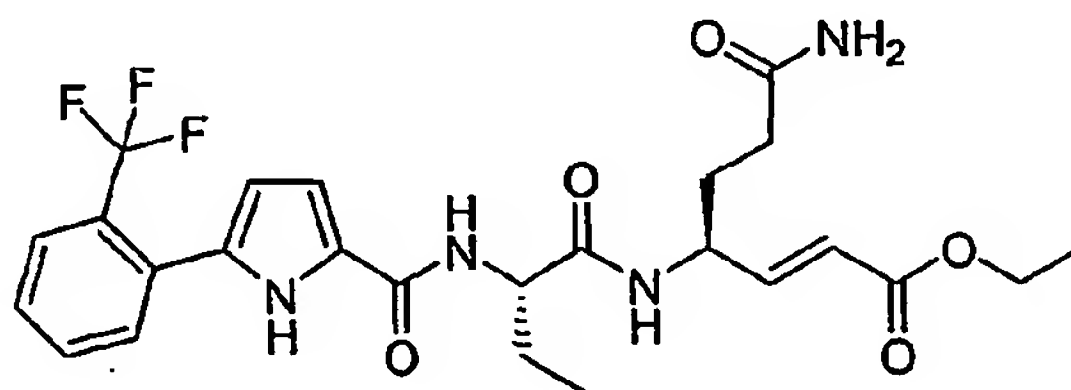
- 115 -

3-Methyl-5-(1H-pyrrol-2-yl)-isoxazole (Sundberg, et al., *J. Org. Chem.*, 1985, 50, 425) was converted to 5-(3-methyl-isoxazol-5-yl)-1H-pyrrole-2-carboxylic acid chloride according to the procedure described in Method 5 of Example 12, then coupled to Phe-Gln resin following Method 1 of Example 2, then cleaved from resin to provide the title compound. ¹H NMR (CD₃OD) δ 7.31-7.19 (6H, m), 6.93 (1H, d, J = 3.9), 6.67 (1H, d, J = 4.0), 6.64 (1H, dd, J = 15.3, 5.7), 6.49 (1H, s), 5.57 (1H, dd, J = 15.8, 0.9), 4.69 (1H, t, J = 15.6), 4.55-4.46 (1H, m), 4.18 (2H, q, J = 7.1), 3.12 (2H, t, J = 7.6), 2.31 (2H, q, J = 8.0), 2.05-1.94 (1H, m), 1.83-1.74 (1H, m), 1.28 (3H, t, J = 7.1). HRMS 544.2163 (MNa⁺, calcd. 544.2172).

10

EXAMPLE 24

6-Carbamoyl-4S-(2S-{[5-(2-trifluoromethyl-phenyl)-1H-pyrrole-2-carbonyl]-amino}-butyrlamino)-hex-2(trans)-enoic acid ethyl ester. (Compound 23)



15

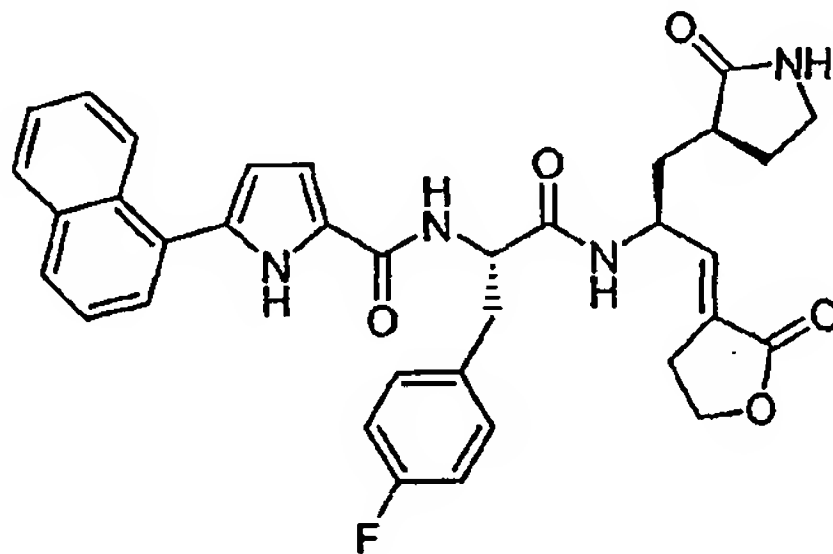
Gln-resin was coupled with Fmoc-aminobutyric acid, deprotected, then coupled to 5-(2-trifluoromethyl-phenyl)-1H-pyrrole-2-carboxylic acid chloride (prepared according to the procedure described in Method 6 of Example 4), following Method 1 of Example 2. ¹H NMR (CDCl₃) δ 10.06 (1H, br s), 7.72 (1H, d, J = 7.7), 7.63-7.37 (4H, m), 7.02 (1H, d, J = 7.5), 6.88-6.76 (2H, m), 6.37 (1H, s), 6.28 (1H, br s), 6.18 (1H, br s), 5.92 (1H, d, J = 15.8), 4.68-4.45 (2H, m), 4.16 (2H, q, J = 7.1), 2.34-2.22 (2H, m), 2.04-1.65 (4H, m), 1.26 (3H, t, J = 7.1), 0.95 (3H, t, J = 7.1). HRMS (MALDI) 545.2002 (MNa⁺, calcd. 545.1988).

20

- 116 -

EXAMPLE 25

5-Naphthalen-1-yl-1H-pyrrole-2-carboxylic acid-{1S-[2-oxo-dihydrofuran-3-ylidene)-1-(2-oxo-pyrrolidin-3S-methyl)-ethyl carbamoyl]-2S-(4-fluoro-phenyl-ethyl))-amide.
(Compound 26)



Method 2 General Experimental: Boc-protected 3S-[2S-amino-3-(2-oxo-dihydro-furan-3-ylidene)-propyl]-pyrrolidin-2-one, prepared by a method analogous to that described in Tian, et al., U.S. Provisional Patent Application No. 60/150,358, filed August 24, 1999 and also Baldwin et al., *J. Org. Chem.*, 1971, 36, 1441, (3.40 mmol, 1.10 g) in CH_2Cl_2 (10 ml) was treated with HCl (17.0 mmol, 4.3 ml of 4M in dioxane), and held at room temperature for 1 h, then concentrated under reduced pressure. The product was diluted with DMF (10 ml), treated with Boc-4-fluoro-phenylalanine (3.40 mmol, 0.96 g), DIEA (10.2 mmol, 1.8 ml), and HATU (3.40 mmol, 1.29 g), then held at room temperature for 1h. The resulting solution was diluted with in ethyl acetate (75 ml), washed with brine (3x20 ml), then concentrated under reduced pressure. The residue was purified by silica gel chromatography to provide 0.84 g (51%) of 2-(4-fluorophenyl)-1S-[2-(2-oxodihydrofuran-3-ylidene)-1-(2-oxo-pyrrolidin-3S-ylmethyl)-ethyl carbamoyl]-ethyl-carbamic acid t-butyl ester. ^1H NMR (CDCl_3) δ 7.82 (1H, br s), 7.15-7.07 (2H, m), 6.96 (2H, t, $J = 8.7$), 6.32 (1H, d, $J = 8.2$), 6.00 (1H, s), 5.22 (1H, d, $J = 7.8$), 4.55-4.32 (4H, m), 3.40-3.28 (2H, m), 3.28-3.10 (1H, m), 3.05-2.95 (2H, m), 2.95-2.83 (1H, m), 2.50-2.20 (2H, m), 2.10-1.90 (1H, m), 1.90-1.70 (2H, m), 1.58-1.46 (1H, m), 1.39 (9H, s).

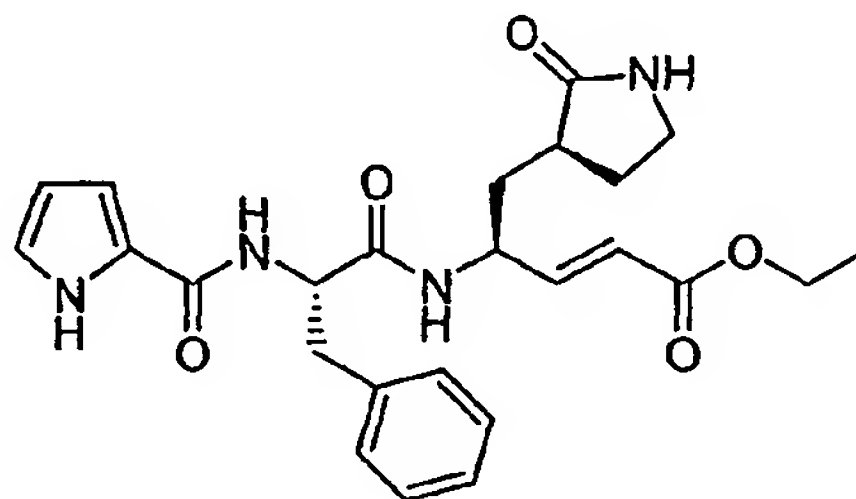
2-(4-Fluorophenyl)-1S-[2-(2-oxodihydrofuran-3-ylidene)-1-(2-oxo-pyrrolidin-3S-ylmethyl)-ethyl carbamoyl]-ethyl-carbamic acid t-butyl ester (0.96 mmol, 0.47 g) in CH_2Cl_2 (5 ml) was treated with HCl (4.8 mmol, 1.2 ml of 4M in dioxane), and held 1 h, then concentrated under reduced pressure. The product was diluted with CH_2Cl_2 (5 ml)

- 117 -

and collidine (2.89 mmol, 0.38 ml), and treated with 5-naphthalene-1-yl-1H-pyrrole-2-carboxylic acid chloride (prepared according to the procedure described in Method 4 of Example 2, starting with 1-naphthalene boronic acid, 0.96 mmol, 0.25 g), then held at room temperature for 1 h. The resulting solution was diluted with ethyl acetate (75 ml), washed with saturated aqueous sodium bicarbonate (2x20 ml) and brine (2x20 ml), then concentrated under reduced pressure. Purification of the residue by silica gel chromatography gave 0.17 g (29%) of product. ¹H NMR (CDCl₃) δ 10.05 (1H, s), 8.27-8.13 (2H, m), 7.92-7.80 (2H, m), 7.57-7.45 (4H, m), 7.20-7.11 (2H, m), 7.05-6.95 (3H, m), 6.73 (1H, d, J = 9.6), 6.51 (1H, dd, J = 3.7, 2.6), 6.32 (1H, DT, J = 8.5, 2.9), 5.36 (1H, br s), 5.15-5.05 (1H, m), 4.46-4.32 (3H, m), 3.42-3.18 (4H, m), 3.02-2.82 (2H, m), 2.36-2.25 (1H, m), 1.90-1.65 (3H, m), 1.60-1.48 (1H, m). HRMS (FAB) 741.1466 (MCs⁺, calcd. 741.1489).

EXAMPLE 26

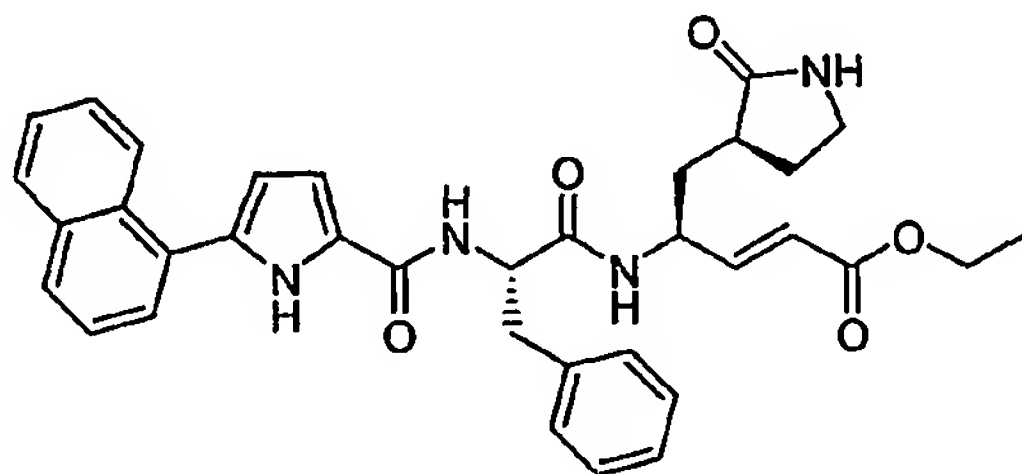
5-(2-Oxo-pyrrolidin-3S-yl)-4S-{3-phenyl-2S-[(1H-pyrrole-2-carbonyl)-amino]-propionylamino}-pent-2(trans)-enoic acid ethyl ester. (Compound 24)



4S-Amino-5-(2-oxo-pyrrolidin-3S-yl)-pent-2(trans)-enoic acid ethyl ester was coupled to Boc-phenylalanine, then deprotected and coupled to pyrrole-2-carboxylic acid chloride, following Method 2 of Example 25. ¹H NMR (CD₃OD) δ 7.23-7.08 (5H, m), 6.82 (1H, dd, J = 2.5, 1.4), 6.71 (1H, dd, J = 3.8, 1.4), 6.58 (1H, dd, J = 10.2, 5.5), 6.13 (1H, dd, J = 3.8, 2.5), 5.57 (1H, dd, J = 15.8, 1.6), 4.74 (1H, t, J = 6.8), 4.47-4.36 (1H, m), 4.10 (2H, q, J = 7.1), 3.11-2.94 (2H, m), 2.27-2.13 (2H, m), 1.84-1.57 (1H, m), 1.49-1.38 (1H, m), 1.21 (3H, t, J = 7.1). HRMS (FAB) 467.2299 (MH⁺, calcd. 467.2294).

EXAMPLE 27

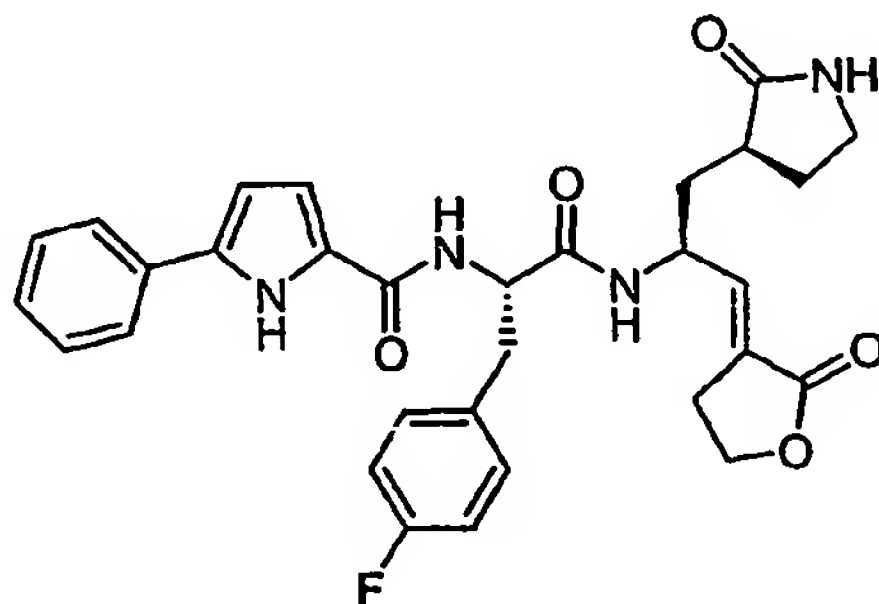
4S-{2S-[(5-Naphthalen-1-yl-1H-pyrrole-2-carbonyl)-amino]-3-phenyl-propionylamino}-5-(2-oxo-pyrrolidin-3S-yl)-pent-2-enoic acid ethyl ester. (Compound 25)



4S-Amino-5-(2-oxo-pyrrolidin-3S-yl)-pent-2(trans)-enoic acid ethyl ester was coupled to Boc-phenylalanine, then deprotected and coupled to 5-naphthalen-1-yl-pyrrole-2-carboxylic acid chloride (prepared according to the procedure described in Method 4 of Example 2, starting with 1-naphthyl boronic acid) following Method 2 of Example 25. ¹H NMR (CDCl₃) δ 10.28 (1H, s), 8.21 (1H, d, J = 9.0), 7.83-7.80 (3H, m), 7.57-7.44 (4H, m), 7.34-7.18 (5H, m), 7.02-6.96 (1H, m), 6.74 (1H, d, J = 9.1), 6.67 (1H, dd, J = 10.2, 5.4), 6.52-6.46 (1H, m), 5.75 (1H, d, J = 15.6), 5.18 (1H, br s), 5.13-5.03 (1H, m), 4.47-4.36 (1H, m), 4.17 (2H, q, J = 7.1), 3.41-3.31 (1H, m), 3.17-3.07 (2H, m), 3.06-2.97 (1H, m), 2.30-2.18 (1H, m), 2.05-1.92 (1H, m), 1.80-1.58 (2H, m), 1.55-1.45 (1H, m), 1.27 (3H, t, J = 7.1). HRMS (FAB) 593.2750 (MH⁺, calcd. 593.2764).

EXAMPLE 28

5-Phenyl-1H-pyrrole-2-carboxylic acid-{2S-(4-fluorophenyl)-1S-[1-(2-oxo-dihydrofuran-3-ylidinemethyl)-1-(2-oxo-pyrrolidin-3S-methyl)-ethyl carbamoyl]-2S-phenyl-ethyl}-amide. (Compound 27)

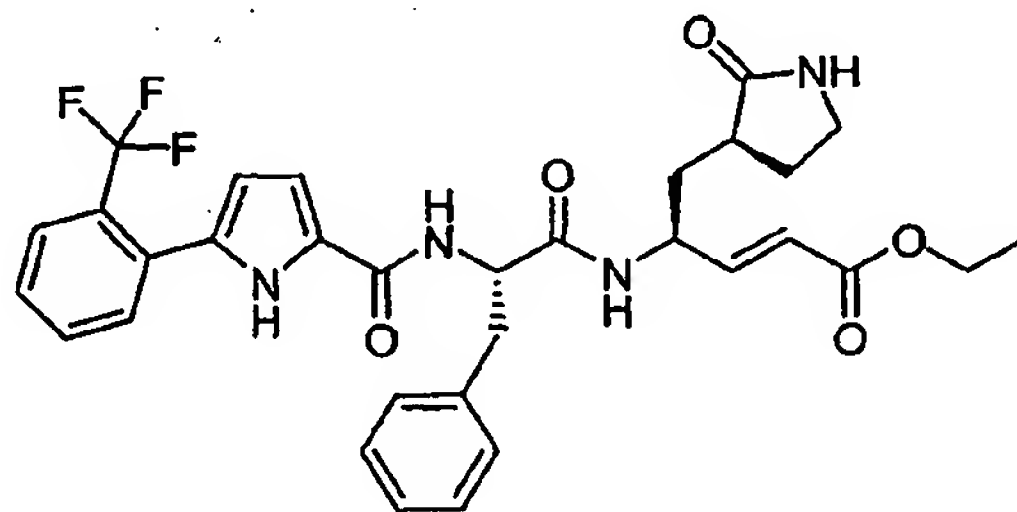


- 119 -

2-(4-Fluorophenyl)-1S-[2-(2-oxodihydrofuran-3-ylidene)-1-(2-oxo-pyrrolidin-3S-ylmethyl)-ethyl carbamoyl]-ethyl-carbamic acid t-butyl ester (prepared as described in Method 2 of Example 25) was deprotected, then coupled to 5-phenyl-1H-pyrrole-2-carboxylic acid chloride (prepared according to the procedure described in Method 5 of Example 12, starting with benzoic acid), following Method 2 of Example 25. ¹H NMR (CDCl₃) δ 10.48 (1H, s), 7.56 (2H, d, J = 7.3), 7.36 (2H, t, J = 7.7), 7.26-7.19 (1H, m), 7.14-7.06 (2H, m), 6.93 (2H, t, J = 8.7), 6.85-6.81 (1H, m), 6.51-6.47 (1H, m), 6.28 (1H, dt, J = 8.8, 3.9), 4.83 (1H, t, J = 5.2), 4.50-4.39 (1H, m), 4.34 (2H, t, J = 7.6), 3.30-3.27 (2H, m), 3.18-2.90 (3H, m), 2.91-2.76 (1H, m), 2.36-2.13 (2H, m), 1.98-1.85 (1H, m), 1.80-1.66 (1H, m), 1.53-1.43 (1H, m). HRMS (FAB) 581.2161 (MNa⁺, calcd. 581.2176).

EXAMPLE 29

5-(2-Oxo-pyrrolidin-3S-yl)-4S-(3-phenyl-2S-{[5-(2-trifluoromethyl-phenyl)-1H-pyrrole-2-carbonyl]-amino}-propionylamino)-pent-2(trans)-enoic acid ethyl ester. (Compound 28)



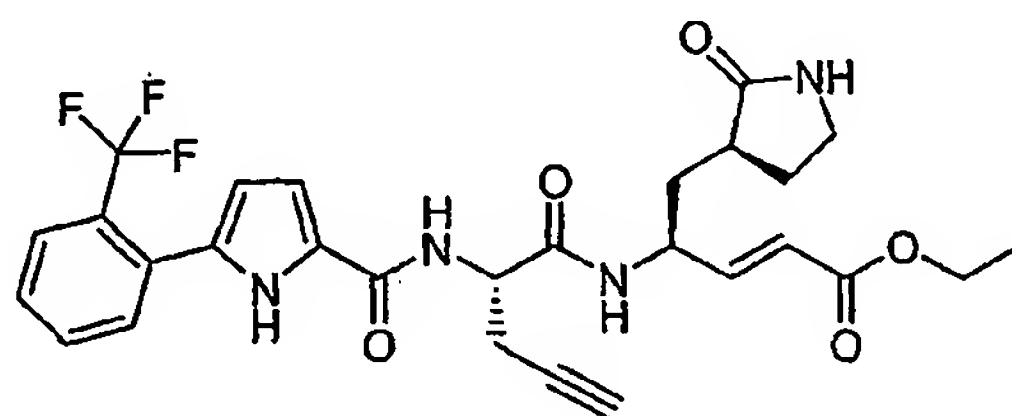
4S-Amino-5-(2-oxo-pyrrolidin-3S-yl)-pent-2(trans)-enoic acid ethyl ester was coupled to Boc-phenylalanine, then deprotected and coupled to 5-(2-trifluoromethyl-phenyl)-1H-pyrrole-2-carboxylic acid chloride (prepared according to the procedure described in Method 6 of Example 4, starting with 2-trifluoromethyl benzaldehyde) following Method 2 of Example 25. ¹H NMR (CDCl₃) δ 10.00 (1H, s), 7.75-7.65 (2H, m), 7.57-7.35 (3H, m), 7.30-7.13 (4H, m), 6.98 (1H, d, J = 8.8), 6.84 (1H, br s), 6.65 (1H, dd, J = 10.2, 5.4), 6.38 (1H, br s), 6.15 (1H, br s), 5.72 (1H, d, J = 14.7), 5.10-4.98 (1H, m), 4.52-4.40 (1H, m), 4.17 (2H, q, J = 7.1), 3.28-3.15 (3H, m), 3.00 (1H, dd, J = 13.4, 7.0), 2.32-2.20 (1H, m), 2.18-2.05 (1H, m), 1.88-1.60 (2H, m), 1.58-1.48 (1H, m),

- 120 -

1.27 (3H, t, J = 7.1). HRMS (MALDI) 611.2475 (MH^+ , calcd. 611.2481). Anal. ($C_{32}H_{33}N_4O_5F_3 \cdot 1.0 H_2O$) C, H, N.

EXAMPLE 30

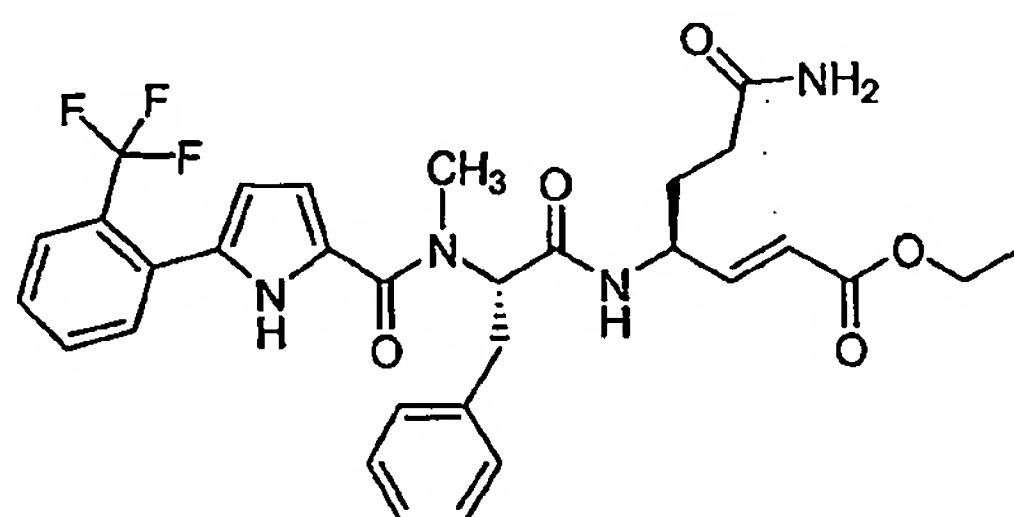
- 5 5-(2-Oxo-pyrrolidin-3S-yl)-4S-(2S-[[5-(2-trifluoromethyl-phenyl)-1H-pyrrole-2-carbonyl]-amino}-pent-4-ynoylamino)-pent-2(trans)-enoic acid ethyl ester. (Compound 29)



- 10 4S-Amino-5-(2-oxo-pyrrolidin-3S-yl)-pent-2(trans)-enoic acid ethyl ester was coupled to Boc-propargyl glycine, then deprotected and coupled to 5-(2-trifluoromethyl-phenyl)-1H-pyrrole-2-carboxylic acid chloride (prepared according to the procedure described in Method 6 of Example 4, starting with 2-trifluoromethyl benzaldehyde) following Method 2 of Example 25. 1H NMR ($CDCl_3$) δ 10.13 (1H, s),
- 15 8.10 (1H, d, J = 7.4), 7.73 (1H, d, J = 7.8), 7.59-7.40 (3H, m), 7.19 (1H, d, J = 8.4), 6.88 (1H, dd, J = 3.8, 2.5), 6.83 (1H, dd, J = 15.7, 5.0), 6.43-6.35 (1H, m), 6.03 (1H, dd, J = 15.7, 1.6), 4.92-4.83 (1H, m), 4.65-4.54 (1H, m), 4.15 (2H, q, J = 7.1), 3.32-3.23 (2H, m), 2.87-2.61 (2H, m), 2.50-2.22 (2H, m), 2.06 (1H, t, J = 2.5), 2.00-1.92 (1H, m), 1.86-1.58 (2H, m), 1.25 (3H, t, J = 7.1). HRMS (MALDI) 581.1992 (MNa^+ ,
- 20 calcd. 581.1988). Anal. ($C_{28}H_{29}N_4O_5F_3 \cdot 0.5 H_2O$) C, H, N.

EXAMPLE 31

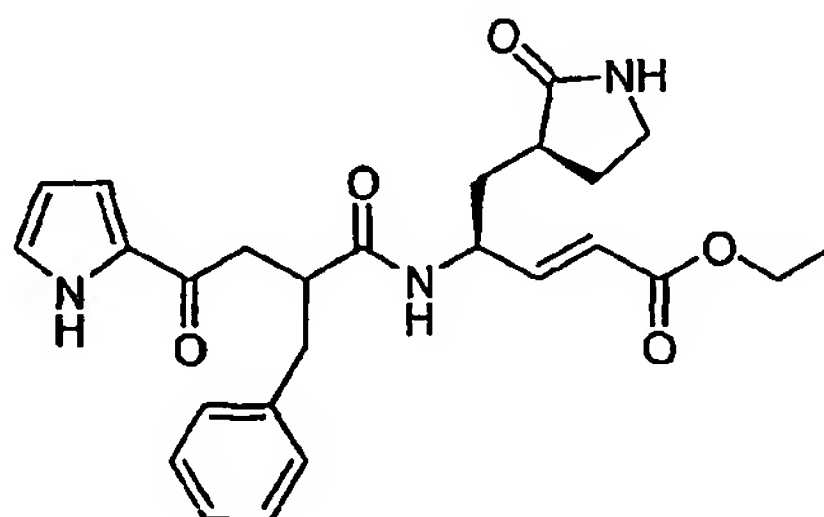
6-Carbamoyl-4S-(2S {methyl-[5-(2-trifluoromethyl-phenyl)-1H-pyrrole-2-carbonyl]-amino}-3-phenyl-propionylamino)-hex-2(trans)-enoic acid ethyl ester. (Compound 41)



Gln-resin was coupled with Fmoc-N-methyl-phenylalanine, according to the procedure described in Method 1 of Example 2, then deprotected and coupled with 5-(2-trifluoromethyl-phenyl)-1H-pyrrole-2-carboxylic acid (prepared according to the procedure described in Method 6 of Example 4), according to the procedure described in Method 1 of Example 2. ¹H NMR (CD₃OD) δ 7.90-7.50 (4H, m), 7.35-7.15 (5H, m), 6.88 (1H, dd, J = 15.8, 5.4), 6.60-6.58 (1H, m), 6.38-6.32 (1H, m), 5.98 (1H, dd, J = 15.8, 1.6), 5.32-5.20 (1H, m), 4.65-4.50 (1H, m), 4.25-4.10 (2H, m), 4.18 (2H, q, J = 7.1), 3.50-3.10 (5H, m), 2.33-2.20 (2H, m), 2.03-1.72 (2H, m), 1.23 (3H, t, J = 7.1). HRMS (MALDI) 621.2301 (MNa⁺, calcd. 621.2301).

EXAMPLE 32

4S-[2(R,S)-Benzyl-4-oxo-4-(1H-pyrrol-2-yl)-butyrylamino-5-(2-oxo-pyrrolidin-3S-yl)-pent-2(trans)-enoic acid ethyl ester.



2(R,S)-Benzyl-4-oxo-4-(1H-pyrrol-2-yl)-butyric acid

Method 7 General Experimental: Pyrrole-2-carboxylic acid (27.0 mmol, 3.00 g) in CH₂Cl₂ (100 ml) was treated with oxalyl chloride (54.0 mmol, 4.70 ml) and DMF

- 122 -

(1 drop), then heated to reflux for 1 h, then concentrated under reduced pressure. The residue was diluted with CH_2Cl_2 (100 ml) and pyridine (6.50 ml), and treated with O,N-dimethyl-hydroxylamine hydrochloride (27.0 mmol, 2.65 g), then held at room temperature overnight. The resulting solution was diluted with ethyl acetate (250 ml),
5 washed with 10% aqueous citric acid (2x30 ml), saturated aqueous sodium bicarbonate (2x30 ml), then brine (2x30 ml). The organics were concentrated under reduced pressure. Purification of the residue by silica gel chromatography provided 3.42 g. (82%) of 1H-pyrrole-2-carboxylic acid methoxy-methyl amide. ^1H NMR (CDCl_3) δ 6.90-6.80 (1H, m), 6.79-6.60 (1H, m), 6.18 (1H, dd, $J = 3.7, 1.3$), 3.81 (3H, s), 3.01
10 (3H, s).

1H-pyrrole-2-carboxylic acid methoxy-methyl amide (22.2 mmol, 3.42 g) in THF (100 ml) was cooled to -78°C , and treated with methyl lithium-lithium bromide complex (44.4 mmol, 29.6 ml of 1.5 M in Et_2O). The solution was held at -78°C for 20 minutes, allowed to warm to 0°C , and held 30 minutes, then poured into saturated
15 aqueous ammonium chloride (300 ml). The mixture was extracted with ethyl acetate (3x150 ml). The combined organic extracts were washed with brine (3x50 ml) and concentrated under reduced pressure. The residue was purified by silica gel chromatography to provide 2.28 g (94%) of 1-(1H-pyrrol-2-yl)-ethanone. ^1H NMR (CDCl_3) δ 7.03 (1H, dt, $J = 2.7, 1.3$), 6.91 (1H, ddd, $J = 3.8, 2.4, 1.3$), 6.30-6.26 (1H, m), 2.44 (3H, s).
20

1-(1H-pyrrol-2-yl)-ethanone (2.67 mmol, 0.29 g) in CH_2Cl_2 (10 ml) and Et_3N (13.3 mmol, 1.90 ml) was cooled to 0°C and treated with trimethylsilyl trifluoromethanesulfonate (5.34 mmol, 1.00 ml). The solution was held at 0°C for 30 minutes, then diluted with ethyl acetate (75 ml) and washed with saturated aqueous
25 sodium bicarbonate (2x20 ml) then brine (30 ml). The solution was concentrated under reduced pressure to provide crude 2-[1-(trimethyl-silanyloxy)-vinyl]-1H-pyrrole. ^1H NMR (CDCl_3) δ 6.77 (1H, dd, $J = 2.7, 1.6$), 6.34 (1H, dd, $J = 3.2, 1.6$), 6.15 (1H, t, $J = 2.8$), 4.56 (1H, d, $J = 1.0$), 4.31 (1H, d, $J = 1.0$), 0.45 (9H, s), 0.25 (9H, s).

Crude 2-[1-(trimethyl-silanyloxy)-vinyl]-1H-pyrrole was diluted with CH_2Cl_2
30 (10 ml), cooled to 0°C , and treated with N-bromosuccinimide (1.94 mmol, 0.35 g). The resulting mixture was put in a -20°C freezer overnight. After warming to room

- 123 -

temperature, the mixture was diluted with ethyl acetate (75 ml), washed with saturated aqueous sodium bicarbonate (2x20 ml), brine (2x20 ml), and the organics concentrated under reduced pressure. Purification of the residue by silica gel chromatography provided 0.29 g (80%) of 2-bromo-1-(1H-pyrrol-2-yl)-ethanone. ¹H NMR (CDCl₃) δ 7.12 (1H, dt, J = 2.7, 1.3), 7.02 (1H, ddd, J = 3.8, 2.4, 1.3), 6.36-6.31 (1H, m), 4.27 (2H, s).

2-Bromo-1-(1H-pyrrol-2-yl)-ethanone (1.00 mmol, 0.19 g) in DME (3 ml) was treated with NaI (1.00 mmol, 0.15 g), and stirred vigorously for 30 minutes. A solution of diethyl malonate (1.50 mmol, 0.2 ml), NaH (1.00 mmol, 40 mg of 60% in oil), and DME (3 ml) was added to the bromide-NaI mixture, and held at room temperature overnight. Saturated aqueous ammonium chloride (10 ml) was added, then the mixture was extracted with ethyl acetate (2x25 ml). The combined organic extracts washed with brine (25 ml), then concentrated under reduced pressure. Purification of the residue by silica gel chromatography provided 0.21 g (79%) of 2-(1H-pyrrole-2-carbonyl)-malonic acid diethyl ester. ¹H NMR (CDCl₃) δ 9.76 (1H, s), 7.04 (1H, dt, J = 2.7, 1.3), 7.00 (1H, ddd, J = 3.8, 2.4, 1.3), 6.30-6.26 (1H, m), 4.21 (4H, m), 4.02 (1H, t, J = 7.3), 3.45 (2H, d, J = 7.3), 1.25 (6H, t, J = 7.1).

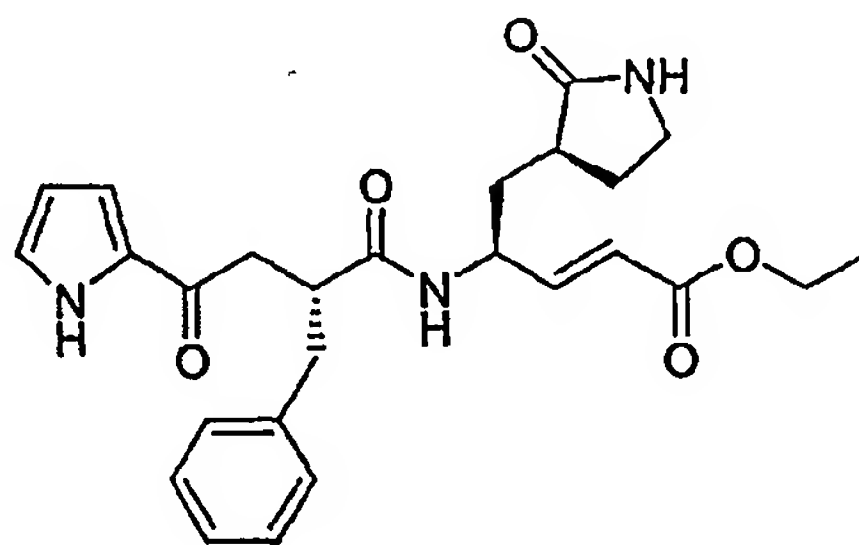
2-(1H-Pyrrole-2-carbonyl)-malonic acid diethyl ester (0.79 mmol, 0.21 g) in DME (3 ml) was treated with lithium bis-trimethylsilylamide (0.79 mmol, 133 mg). The resulting solution was held at room temperature for 30 minutes, then treated with benzyl bromide (0.79 mmol, 0.10 ml). The resulting solution was held at room temperature overnight, then diluted with ethyl acetate (30 ml), and washed with saturated ammonium chloride (10 ml), followed by brine (20 ml). The organics were concentrated under reduced pressure and the residue was purified by silica gel chromatography to provide 0.23 g (84%) of 2-benzyl-2-(1H-pyrrole-2-carbonyl)-malonic acid diethyl ester. ¹H NMR (CDCl₃) δ 10.01 (1H, s), 7.25-7.17 (4H, m), 7.14 (1H, dt, J = 2.7, 1.3), 7.03-6.98 (1H, m), 6.86 (1H, ddd, J = 3.8, 2.4, 1.3), 6.29-6.25 (1H, m), 4.22 (4H, q, J = 7.1), 3.47 (2H, s), 3.39 (2H, s), 1.25 (6H, t, J = 1.7).

2-Benzyl-2-(1H-pyrrole-2-carbonyl)-malonic acid diethyl ester (0.66 mmol, 0.23 g) in 1:1 dioxane-water (10 ml) was treated with lithium hydroxide (1.31 mmol, 31 mg), then heated to reflux for 30 minutes. The solution was treated with saturated

- 124 -

aqueous citric acid (20 ml), extracted with ethyl acetate (30 ml). The organic extract was washed with brine (15 ml) then concentrated under reduced pressure. The residue was purified by silica gel chromatography to provide 0.11 g (64%) of 2(R,S)-benzyl-4-oxo-4-(1H-pyrrol-2-yl)-butyric acid. ¹H NMR (CDCl₃) δ 7.18-7.04 (5H, m), 6.92 (1H, dd, J = 2.4, 1.4), 6.80 (1H, dd, J = 3.8, 1.3), 6.08 (1H, dd, J = 3.8, 2.5), 3.20-2.85 (3H, m), 2.80-2.67 (2H, m).

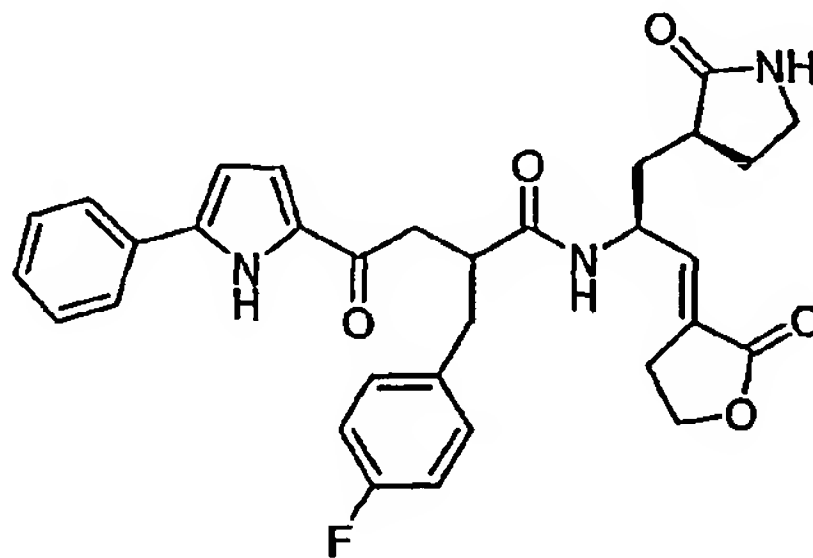
Method 3 General Experimental: 2(R,S)-Benzyl-4-oxo-4-(1H-pyrrol-2-yl)-butyric acid (0.42 mmol, 0.11 g, prepared according to the procedure described in Example 7), 4S-amino-5-(2-oxo-pyrrolidin-3S-yl)-pent-2(trans)-enoic acid ethyl ester hydrochloride (0.42 mmol, 0.11 g), and DIEA (1.26 mmol, 0.22 ml) in DMF (2 ml) were treated with HATU (0.42 mmol, 0.16 g), then held at room temperature overnight. The resulting solution was diluted with ethyl acetate (30 ml), washed with brine (2x15 ml). The organics were concentrated under reduced pressure and the residue was purified by silica gel chromatography to provide 0.14 g (75%) of product. The diastereomers were separated by preparative reverse phase HPLC (CH₃CN-water gradient).



2R-Benzyl diastereomer (Compound 30): ¹H NMR (CDCl₃) δ 11.05 (1H, s), 7.40 (1H, d, J = 8.0), 7.32-7.15 (5H), 7.05 (1H, ddd, J = 3.8, 2.4, 1.3), 7.00-6.96 (2H, m), 6.52 (1H, dd, J = 15.7, 5.0), 6.27-6.23 (1H, m), 5.32 (1H, dd, J = 15.7, 1.6), 4.44-4.32 (1H, m), 4.14 (2H, q, J = 7.1), 3.53 (1H, dd, J = 14.4, 10.9), 3.34-3.02 (4H, m), 2.85 (1H, dd, J = 13.1, 4.9), 2.57 (1H, dd, J = 14.5, 3.1), 2.20-2.08 (1H, m), 1.98-1.84 (1H, m), 1.72-1.60 (1H, m), 1.60-1.41 (1H, m), 1.40-1.28 (1H, m), 1.28 (3H, t, J = 7.1). HRMS (FAB) 466.2234 (MH⁺, calcd. 466.2342).

EXAMPLE 33

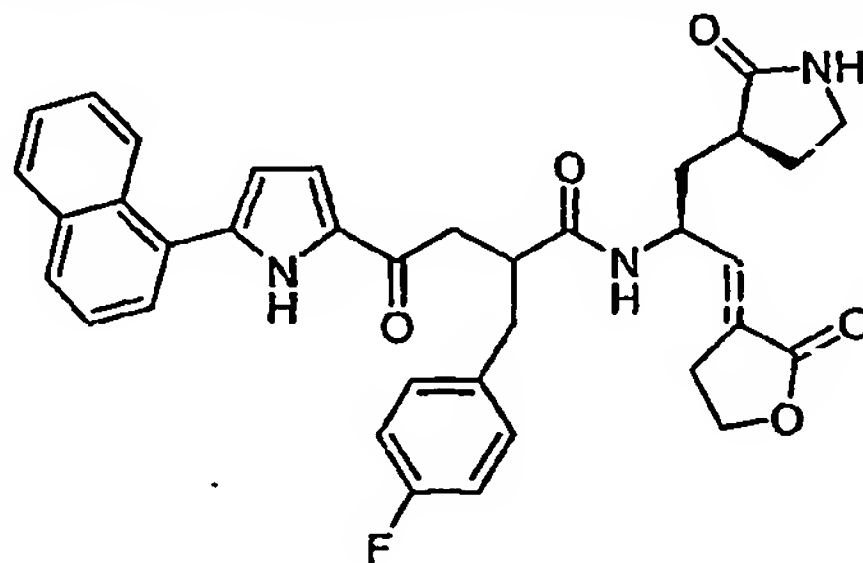
2-(R,S)-(4-Fluorobenzyl)-4-oxo-N-[2-(2-oxo-dihydro-furan-3-ylidene)-1S-(2-oxo-pyrrolidin-3S-ylmethyl)-ethyl]-4-(5-phenyl-1H-pyrrol-2-yl)-butyramide. (Compound 31)



2-(R,S)-(4-Fluorobenzyl)-4-oxo-4-(5-phenyl-1H-pyrrol-2-yl)-butyric acid was prepared according to the procedure described in Example 7, starting with 5-phenyl-1H-pyrrole-2-carboxylic acid (prepared according to the procedure described in Example 4, starting with phenylboronic acid). This material was coupled to 3S-[2S-amino-3-(2-oxo-dihydro-furan-3-ylidene)-propyl] pyrrolidin-2-one hydrochloride according to the procedure described in Method 3 of Example 31, to provide the title compound as a 1:1 mixture of 2R-2S diastereomers. ¹H NMR (CDCl₃) δ 10.24 (0.5 H, br s), 9.90 (0.5 H, br s), 7.70-6.85 (11 H, m), 6.61-6.54 (1H, m), 6.37-6.27 (1H, m), 6.27-6.18 (1H, m), 4.50-4.13 (3H, m), 3.42-2.60 (9H, m), 2.25-1.20 (5H, m). HRMS (FAB) 580.2228 (MNa⁺, calcd. 580.2224).

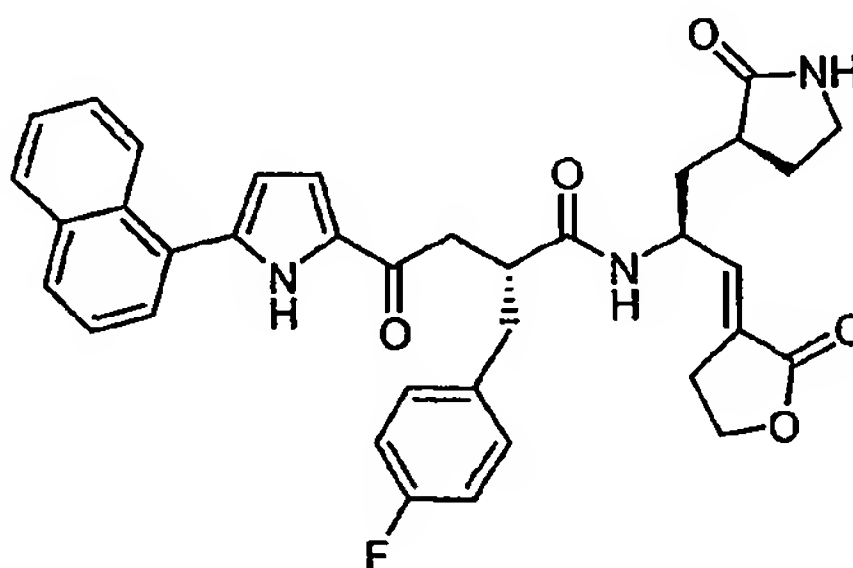
EXAMPLE 34

2-(R,S)-(4-Fluorobenzyl)-4-(5-naphthalen-1-yl-1H-pyrrol-2-yl)-4-oxo-N-[2-(2-oxo-dihydro-furan-3-ylidene)-1S-(2-oxo-pyrrolidin-3S-ylmethyl)-ethyl]-butyramide.

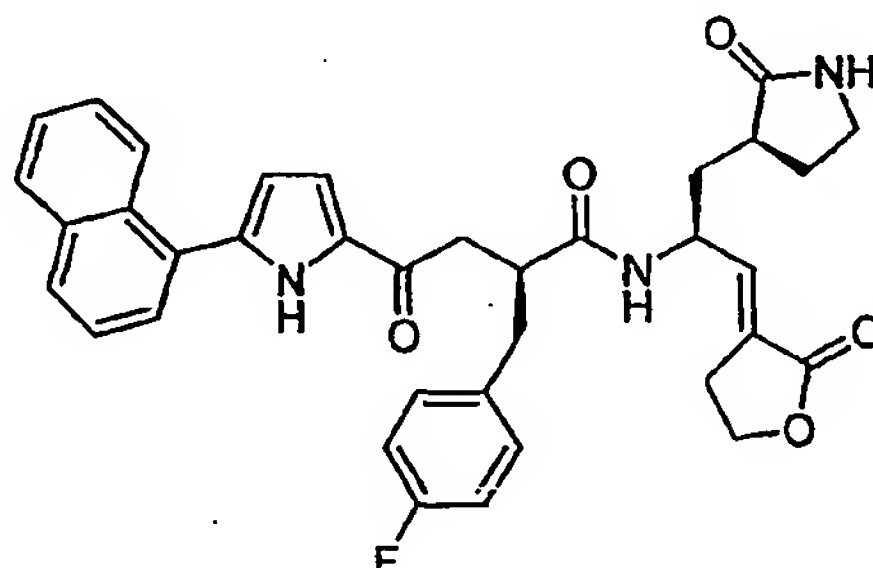


- 126 -

2-(R,S)-(4-Fluorobenzyl)-4-oxo-4-(5-naphthalen-1-yl-1H-pyrrol-2-yl)-butyric acid was prepared according to the procedure described in Example 7, starting with 5-naphthalen-1-yl-1H-pyrrole-2-carboxylic acid (prepared according to the procedure described in Example 4, starting with 1-naphthylboronic acid). This material was coupled to 3S-[2S-amino-3-(2-oxo-dihydro-furan-3-ylidene)-propyl] pyrrolidin-2-one hydrochloride according to the procedure described in Method 3 of Example 31, to provide the title compound as a 1:1 mixture of 2R-2S diastereomers. The diastereomers were separated by preparative reverse phase chromatography (acetonitrile-H₂O gradient).



2R-(4-Fluorobenzyl) diastereomer (Compound 33): ¹H NMR (CDCl₃) δ 10.48 (1H, s), 8.07 (1H, d, J = 8.2), 7.87 (1H, d, J = 7.8), 7.82 (1H, d, J = 8.1), 7.70 (1H, d, J = 5.6), 7.55-7.30 (4H, m), 7.15-7.02 (3H, m), 6.98-6.89 (2H, m), 6.55 (1H, br s), 6.48 (1H, br s), 6.22 (1H, d, J = 8.5), 4.40-4.28 (3H, m), 3.80-1.30 (14H, m). HRMS (FAB) 740.1512 (MCs⁺, calcd. 740.1537).



(4:1 mixture)

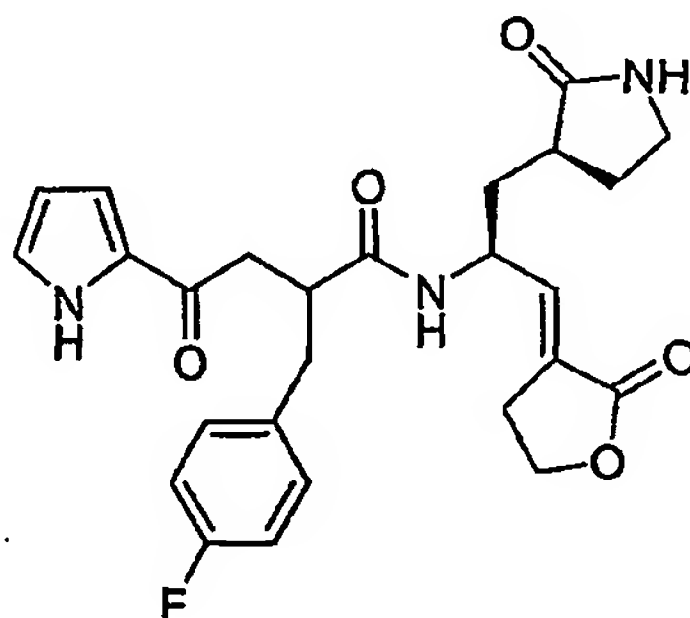
2S-(4-Fluorobenzyl) diastereomer (Compound 32): ¹H NMR (CDCl₃) δ 9.81 (1H, br s), 8.04 (1H, d, J = 8.6), 7.85-7.68 (3H, m), 7.52-7.35 (4H, m), 7.20-6.85 (5H,

- 127 -

m), 6.50-6.25 (3H, m), 4.35-4.18 (3H, m), 3.28-2.60 (9H, m), 2.20-1.85 (2H, m), 1.70-1.55 (2H, m), 1.40-1.22 (1H, m). HRMS (FAB) 740.1512 (MCs⁺, calcd. 740.1537).

EXAMPLE 35

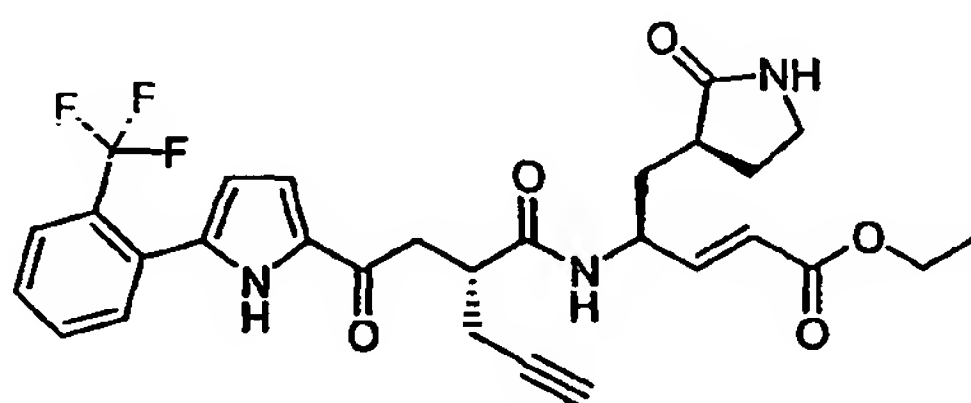
5 2-(R,S)-(4-Fluorobenzyl)-4-oxo-N-[2-(2-oxo-dihydro-furan-3-ylidene)-1S-(2-oxo-pyrrolidin-3S-ylmethyl)-ethyl]-4-(1H-pyrrol-2-yl)-butyramide. (Compound 34)



2-(R,S)-(4-Fluorobenzyl)-4-oxo-4-(1H-pyrrol-2-yl)-butyric acid) was prepared
 10 according to the procedure described in Example 7, starting with 2-pyrrolicarboxylic
 acid. This material was coupled to 3S-[2S-amino-3-(2-oxo-dihydro-furan-3-ylidene)-
 propyl] pyrrolidin-2-one hydrochloride according to the procedure described in Method
 3 of Example 31, to provide the title compound as a 1:1 mixture of 2R-2S
 diastereomers. ¹H NMR (CDCl₃) δ 10.62 (0.5H, br s), 10.12 (0.5H, br s), 7.83 (0.5H, d,
 15 J = 7.7), 7.62 (0.5H, d, J = 7.1), 7.20-6.82 (6H, m), 6.65-6.20 (3H, m), 4.50-4.20 (3H,
 m), 3.45-2.60 (9H, m), 2.25-1.90 (3H, m), 1.68-1.50 (1H, m), 1.42-1.20 (1H, m).
 HRMS (FAB) 504.1932 (MNa⁺, calcd. 504.1911).

EXAMPLE 36

20 5-(2-Oxo-pyrrolidine-3S-yl)-4S-(2R-{2-oxo-2-[5-(2-trifluoromethyl-phenyl)-1H-pyrrol-
 2-yl]-ethyl}-pent-4-ynoylamino-pent-2(trans)-enoic acid ethyl ester.
 (Compound 36)



- 128 -

Method 8 General Experimental: 4-Pentynoic acid (60.1 mmol, 5.90 g) in THF (140 ml) was cooled to -78°C , then treated with Et_3N (69.1 mmol, 9.60 ml), followed by pivaloyl chloride (61.9 mmol, 7.6 ml). The resulting mixture was allowed to warm to 0°C , held 30 minutes, then re-cooled to -78°C . A solution of 4S-isopropyl-2-oxazolidinone (60.1 mmol, 7.76 g) in THF (140 ml) was cooled to -78°C and treated with butyllithium (61.9 mmol, 24.8 ml of 2.5M in hexanes), held at -78°C for 30 minutes, then transferred via cannula at -78°C into the 4-pentynoic acid-pivaloyl chloride solution. The mixture was held at -78°C for 1h, then warmed to 0°C and held 30 minutes, then poured into saturated aqueous ammonium chloride (200 ml). The solution was extracted with ethyl acetate (3x150 ml). The combined organic extracts were washed with brine (2x50 ml), then concentrated under reduced pressure to give 12.8 g of 4S-isopropyl-3-pent-4-ynoyl-oxazolidin-2-one, which may be used without further purification. ^1H NMR (CDCl_3) δ 4.44-4.37 (1H, m), 4.29-4.15 (2H, m), 3.23-3.01 (2H, m), 2.50 (2H, dt, $J = 7.1, 2.6$), 2.39-2.27 (1H, m), 1.93 (1H, t, $J = 2.6$), 0.87 (3H, d, $J = 7.0$), 0.82 (3H, d, $J = 6.9$).

4S-Isopropyl-3-pent-4-ynoyl-oxazolidin-2-one (7.50 mmol, 2.11 g) in THF (25 ml) was cooled to -78°C and treated with a solution of lithium bis(trimethylsilyl)amide (8.25 mmol, 1.38 g) in THF (5 ml). The resulting solution was allowed to warm to 0°C , held 15 minutes, then re-cooled to -78°C , then treated with t-butyl bromoacetate (22.5 mmol, 3.3 ml). The resulting solution was held at -78°C for 15 minutes, then warmed to 0°C and held for 2 h. The solution was then poured into saturated aqueous ammonium acetate (30 ml), then extracted with ethyl acetate (2x50 ml). The combined organic extracts were washed with brine (2x15 ml), then concentrated under reduced pressure. The residue was purified by silica gel chromatography to provide 1.23 g (43%) of 3R-(4S-isopropyl-2-oxo-oxazolidine-3-carbonyl)-hex-5-ynoic acid t-butyl ester. ^1H NMR (CDCl_3) δ 4.46-4.39 (1H, m), 4.35-4.16 (3H, m), 2.87 (1H, dd, $J = 16.7, 9.8$), 2.59-2.27 (4H, m), 2.00 (1H, t, $J = 2.6$), 1.39 (9H, s), 0.90 (3H, d, $J = 3.9$), 0.87 (3H, d, $J = 4.0$).

3R-(4S-Isopropyl-2-oxo-oxazolidine-3-carbonyl)-hex-5-ynoic acid t-butyl ester (10.12 mmol, 3.27 g) in THF (100 ml) and H_2O (50 ml) was cooled to 0°C and treated with lithium hydroxide hydrate (20.2 mmol, 0.85 g), followed by H_2O_2 (41.5 mmol,

- 129 -

4.7 ml of 30% aqueous). The resulting solution was held at 0 °C for 1 h, then allowed to warm to room temperature and held 3 h. The solution was then cooled to 0 °C, and quenched with saturated aqueous sodium bisulfite (30 ml). The solution was acidified with saturated aqueous citric acid (30 ml), and extracted with ethyl acetate (75 ml).

- 5 The organic extract was washed with brine (30 ml), then concentrated under reduced pressure. The residue was purified by silica gel chromatography to provide 2R-prop-2-ynyl-succinic acid-4-t-butyl ester. This material was treated with diazomethane (30 mmol, generated from N-nitroso-N-methyl urea), then concentrated under reduced pressure to give 1.95 g of 2R-prop-2-ynyl-succinic acid 4-t-butyl ester 1-methyl ester.
- 10 This material was treated with 20% TFA -CH₂Cl₂ (30 ml), held 30 min, then concentrated under reduced pressure to give 1.47 g (85%) of 2R-prop-2-ynyl-succinic acid-1-methyl ester. ¹H NMR (CDCl₃) δ 10.12 (1H, br s), 3.08-2.50 (5H, m), 3.73 (3H, s), 2.05 (1H, t, J = 2.7).

- 2R-Prop-2-ynyl-succinic acid -1-methyl ester (8.63 mmol, 1.47 g) in CH₂Cl₂
- 15 (30 ml) was treated with oxalyl chloride (17.3 mmol, 1.50 ml) and DMF (1 drop), then heated to reflux for 30 minutes, then concentrated under reduced pressure. The residue was diluted with CH₂Cl₂ (30 ml), and pyridine (43.2 mmol, 3.5 ml), then treated with dimethylamine hydrochloride (25.9 mmol, 2.11 g), and held at room temperature overnight. The resulting mixture was diluted with ethyl acetate (150 ml) and washed
- 20 with brine (3x30 ml). The organics were concentrated under reduced pressure. Purification of the residue by silica gel chromatography provided 0.83 g (49%) of 2R-dimethylcarbamoylmethyl-pent-4-ynoic acid methyl ester. ¹H NMR (CDCl₃) δ 3.69 (3H, s), 3.18-2.52 (11H, m), 2.00 (1H, t, J = 2.7).

- 2R-Dimethylcarbamoylmethyl-pent-4-ynoic acid methyl ester (4.20 mmol, 0.89 g) was cooled to 0 °C and treated with POCl₃ (4.2 mmol, 0.40 ml). The mixture
- 25 was allowed to warm to room temperature, and held for 1h then diluted with ethylene dichloride (10 ml), and re-cooled to 0 °C. 2-(2-Trifluoromethyl-phenyl)-1H-pyrrole (4.2 mmol, 0.89 g, prepared according to the procedure described in Example 6) in ethylene dichloride (10 ml) was added, and the mixture was allowed to warm to room
- 30 temperature, then heated to reflux for 2 h. The mixture was then allowed to cool to room temperature, then treated with saturated aqueous sodium acetate (10 ml), and

- 130 -

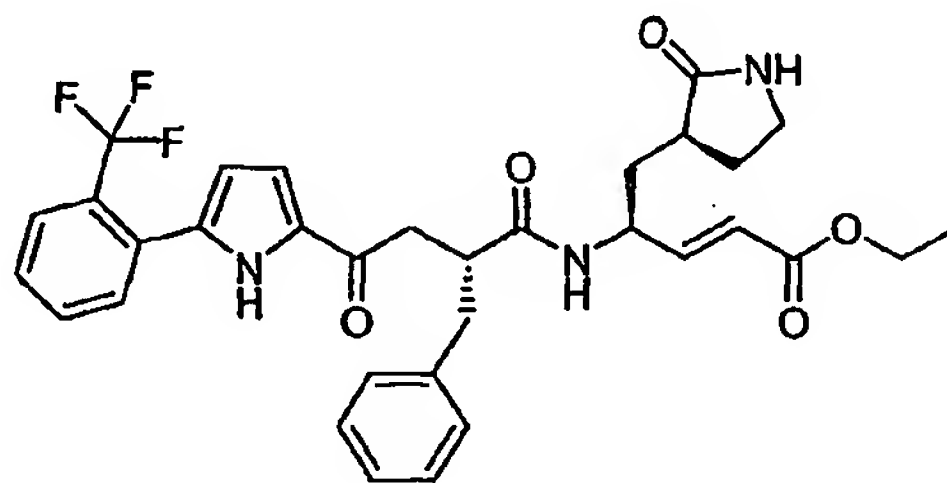
heated to reflux for 15 minutes. The solution was then carefully neutralized with saturated aqueous sodium bicarbonate (20 ml), and extracted with ethyl acetate (75 ml). The organic extract was washed with brine (25 ml), then concentrated under reduced pressure. The residue was purified by silica gel chromatography to provide 1.11 g
5 (72 %) of 2R-(2-oxo-2-[5-(2-trifluoromethyl-phenyl)-1H-pyrrol-2-yl]-ethyl)-pent-4-ynoic acid methyl ester. ¹H NMR (CDCl₃) δ 9.50 (1H, br s), 7.78 (1H, d, J = 7.4), 7.64-7.46 (3H, m), 7.02 (1H, dd, J = 3.9, 2.5), 6.45 (1H, t, J = 3.0), 3.72 (3H, s), 3.45-3.14 (3H, m), 2.62 (1H, d, J = 2.7), 2.59 (1H, d, J = 2.6), 2.04 (1H, t, J = 2.7). This material was diluted with 1:1 H₂O-dioxane (40 ml), and treated with lithium hydroxide hydrate
10 (9.18 mmol, 0.38 g), then heated to reflux for 30 minutes. The solution was acidified with saturated aqueous citric acid (20 ml), extracted with ethyl acetate (3x30 ml). The combined organic extracts were washed with brine (3x20 ml), then concentrated under reduced pressure. The residue was purified by silica gel chromatography to provide 0.67 g (60 %) of 2R-(2-oxo-2-[5-(2-trifluoromethyl-phenyl)-1H-pyrrol-2-yl]-ethyl)-
15 pent-4-ynoic acid.

2R-(2-oxo-2-[5-(2-trifluoromethyl-phenyl)-1H-pyrrol-2-yl]-ethyl)-pent-4-ynoic acid was coupled with 4S-amino-5-(2-oxo-pyrrolidin-3S-yl)-pent-2(trans)-enoic acid ethyl ester hydrochloride according to the procedure described in Method 3 of Example 31. ¹H NMR (CD₃OD) δ 10.31 (1H, br s), 7.73 (1H, d, J = 7.9), 7.61-7.42 (3H, m),
20 6.99 (1H, d, J = 4.0), 6.82 (1H, dd, J = 15.7, 4.6), 6.39 (1H, d, J = 3.8), 6.04 (1H, dd, J = 15.7, 1.6), 4.64-4.54 (1H, m), 4.13 (2H, q, J = 7.1), 3.38-2.92 (5H, m), 2.62-2.38 (3H, m), 2.25-2.12 (1H, m), 2.10 (1H, t, J = 2.6), 2.05-1.89 (1H, m), 1.75-1.60 (1H, m), 1.60-1.48 (1H, m), 1.24 (3H, t, J = 7.1). HRMS (MALDI) 558.2221 (MH⁺, calcd. 558.2216). Anal. (C₂₉H₃₀N₃O₅F₃ · 0.3 H₂O) C, H, N.

- 131 -

EXAMPLE 37

4S-{2R-Benzyl-4-oxo-4-[5-(2-trifluoromethyl-phenyl)-1H-pyrrol-2-yl]-butyrylamino}-5-(2-oxo-pyrrolidin-3S-yl)-pent-2(trans)-enoic acid ethyl ester. (Compound 35)



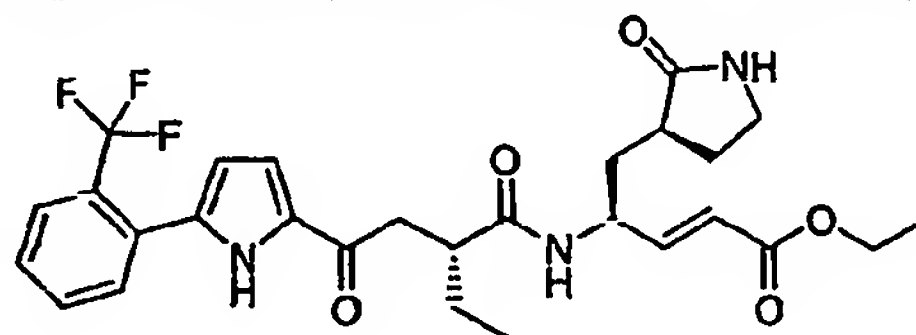
5

2R-Benzyl-N,N-dimethyl-succinamic acid was prepared according to the procedure described in Example 8, starting with hydrocinnamic acid. This material was reacted with 2-(2-trifluoromethyl-phenyl)-1H-pyrrole (prepared according to the procedure described in Example 6), then demethylated to give 2R-benzyl-4-oxo-4-[5-(2-trifluoromethyl-phenyl)-1H-pyrrol-2-yl]-butyric acid (all following Method 8). This material was coupled to 4S-amino-5-(2-oxo-pyrrolidin-3S-yl)-pent-2(trans)-enoic acid ethyl ester hydrochloride according to the procedure described in Method 3 of Example 31. ¹H NMR (CDCl₃) δ 10.01 (1H, br s), 7.72 (1H, d, J = 7.7), 7.55-7.40 (3H, m), 7.34-7.16 (5H, m), 6.98 (1H, dd, J = 3.9, 2.4), 6.90 (1H, d, J = 7.4), 6.62 (1H, dd, J = 15.7, 5.1), 6.41 (1H, t, J = 3.2), 6.13 (1H, br s), 5.49 (1H, dd, J = 15.7, 1.6), 4.56-4.44 (1H, m), 4.16 (2H, q, J = 7.1), 3.39 (1H, dd, J = 16.1, 9.5), 3.25-2.96 (4H, m), 2.83-2.69 (2H, m), 2.42-2.28 (1H, m), 2.22-2.08 (1H, m), 1.94-1.78 (1H, m), 1.72-1.55 (1H, m), 1.52-1.40 (1H, m), 1.30 (3H, t, J = 7.1). HRMS (MALDI) 610.2532 (MH⁺, calcd. 610.2529). Anal. (C₃₃H₃₄F₃N₃O₅) C, H, N.

20

EXAMPLE 38

4S-{2R-Ethyl-4-oxo-4-[5-(2-trifluoromethyl-phenyl)-1H-pyrrol-2-yl]-butyrylamino}-5-(2-oxo-pyrrolidin-3S-yl)-pent-2(trans)-enoic acid ethyl ester. (Compound 37)



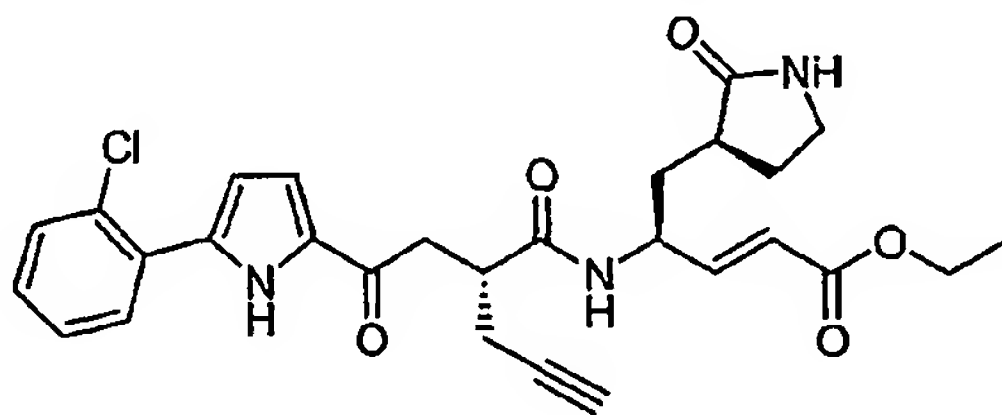
25

2R-Ethyl-N,N-dimethyl-succinamic acid methyl ester was prepared according to the procedure described in Example 8, starting with butyric acid. This was reacted with 2-(2-trifluoromethyl-phenyl)-1H-pyrrole (prepared according to the procedure described in Example 6), then demethylated to give 2R-ethyl-4-oxo-4-[5-(2-trifluoromethyl-phenyl)-1H-pyrrol-2-yl]-butyric acid (all following Method 8). This material was then coupled to 4S-amino-5-(2-oxo-pyrrolidin-3S-yl)-pent-2(trans)-enoic acid ethyl ester hydrochloride according to the procedure described in Method 3 of Example 31. ¹H NMR (CDCl₃) δ 10.13 (1H, br s), 7.76 (1H, d, J = 7.8), 7.62-7.46 (3H, m), 7.01 (1H, d, J = 3.9), 6.84 (1H, dd, J = 15.7, 5.2), 6.42 (1H, d, J = 3.9), 5.93 (1H, dd, J = 15.3, 1.6), 4.70-4.60 (1H, m), 4.17 (2H, q, J = 7.1), 3.36-3.15 (3H, m), 2.86-2.70 (2H, m), 2.58-2.53 (1H, m), 2.33-2.23 (1H, m), 2.05-1.94 (1H, m), 1.83-1.74 (2H, m), 1.61-1.51 (2H, m), 1.27 (3H, t, J = 7.1), 1.01 (3H, t, J = 7.3). HRMS (MALDI) 548.2363 (MH⁺, calcd. 548.2372). Anal. (C₂₈H₃₂N₃O₅F₃·0.7 H₂O) C, H, N.

15

EXAMPLE 39

4S-(2R-{2-[5-(2-Chloro-phenyl)-1H-pyrrol-2-yl]-2-oxo-ethyl}-pent-4-ynoylamino)-5-(2-oxo-pyrrolidin-3S-yl)-pent-2(trans)-enoic acid ethyl ester. (Compound 38)



20

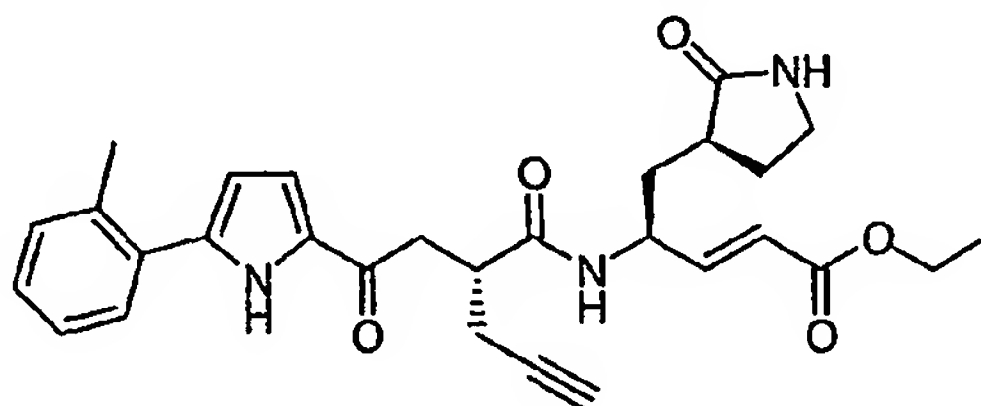
2R-Dimethylcarbamoylmethyl-pent-4-ynoic acid methyl ester was prepared according to the procedure described in Example 8, starting with 4-pentynoic acid. This material was reacted with 2-(2-chloro-phenyl)-1H-pyrrole (prepared according to the procedure described in Example 6, starting with 2-chlorobenzaldehyde). This product was demethylated to give 2R-{2-[5-(2-chloro-phenyl)-1H-pyrrol-2-yl]-2-oxo-ethyl}-pent-4-ynoic acid (all following Method 8), then coupled to 4S-amino-5-(2-oxo-pyrrolidin-3S-yl)-pent-2(trans)-enoic acid ethyl ester hydrochloride according to the procedure described in Method 3 of Example 31. ¹H NMR (CDCl₃) δ 10.58 (1H, br s), 7.65 (1H, d, J = 7.4), 7.56 (1H, dd, J = 7.6, 1.8), 7.46 (1H, dd, J = 7.7, 1.4), 7.37-7.23

- 133 -

(2H, m), 7.07 (1H, dd, J = 4.0, 2.4), 6.83 (1H, dd, J = 15.6, 4.7), 6.68 (1H, dd, J = 4.0, 2.6), 6.28 (1H, br s), 6.05 (1H, dd, J = 15.7, 1.6), 4.58-4.46 (1H, m), 4.15 (2H, q, J = 7.1), 3.38 (1H, dd, J = 15.3, 9.8), 3.15 (1H, t, J = 9.1), 3.10-2.95 (2H, m), 2.87 (1H, dd, J = 15.3, 3.7), 2.63 (1H, ddd, J = 16.8, 7.3, 2.6), 2.47 (1H, ddd, J = 16.8, 7.5, 2.6), 2.28-2.15 (1H, m), 2.10 (1H, t, J = 2.5), 2.06-1.88 (2H, m), 1.73-1.50 (2H, m), 1.26 (3H, t, J = 7.1). HRMS (MALDI) 546.1750 (MNa⁺, calcd. 546.1722). Anal. (C₂₈H₃₀N₃O₅Cl · 0.6 H₂O) C, H, N.

EXAMPLE 40

5-(2-Oxo-pyrrolidin-3S-yl)-4S-{2R-[2-oxo-2-(5-o-tolyl-1H-pyrrol-2-yl)-ethyl]-pent-4-ynoylamino}-pent-2(trans)-enoic acid ethyl ester. (Compound 39)

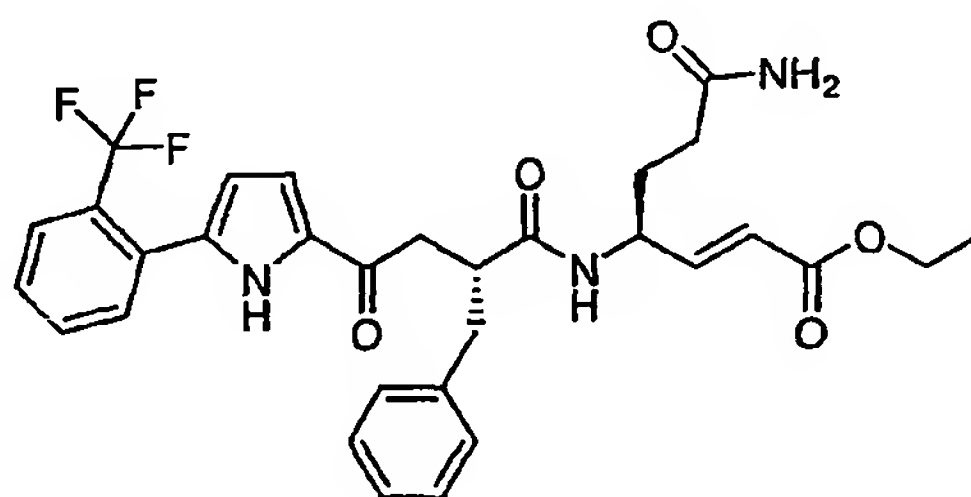


2R-Dimethylcarbamoylmethyl-pent-4-ynoic acid methyl ester was prepared according to the procedure described in Example 8, starting with 4-pentynoic acid. This material was reacted with 2-(o-tolyl)-1H-pyrrole (prepared according to the procedure described in Example 5, starting with o-toluic acid). This product was demethylated to give 2R-[2-oxo-2-(5-o-tolyl-1H-pyrrol-2-yl)-ethyl]-pent-4-ynoic acid (all following Method 8), then coupled to 4S-amino-5-(2-oxo-pyrrolidin-3S-yl)-pent-2(trans)-enoic acid ethyl ester hydrochloride according to the procedure described in Method 3 of Example 31. ¹H NMR (CDCl₃) δ 10.65 (1H, br s), 7.50 (1H, d, J = 7.6), 7.43-7.36 (1H, m), 7.30-7.21 (3H, m), 7.10-7.04 (1H, m), 6.82 (1H, dd, J = 15.6, 5.4), 6.47 (1H, br s), 6.39-6.33 (1H, m), 6.04 (1H, d, J = 15.6), 4.59-4.48 (1H, m), 4.15 (2H, q, J = 7.1), 3.39 (1H, dd, J = 15.4, 10.4), 3.12-2.95 (2H, m), 2.95-2.77 (2H, m), 2.68-2.55 (1H, m), 2.51-2.38 (1H, m), 2.40 (3H, s), 2.36-2.25 (1H, m), 2.12 (1H, br s), 2.03-1.90 (1H, m), 1.66-1.43 (2H, m), 1.26 (3H, t, J = 7.1). HRMS (MALDI) 504.2497 (MH⁺, calcd. 504.2498). Anal. (C₂₉H₃₃N₃O₅ · 0.7 H₂O) C, H, N.

- 134 -

EXAMPLE 41

4S-{2R-Benzyl-4-oxo-[5-(2-trifluoromethyl-phenyl)-1H-pyrrol-2-yl]-butyrylamino}-6-carbamoyl-hex-2(trans)-enoic acid ethyl ester. (Compound 40)



5

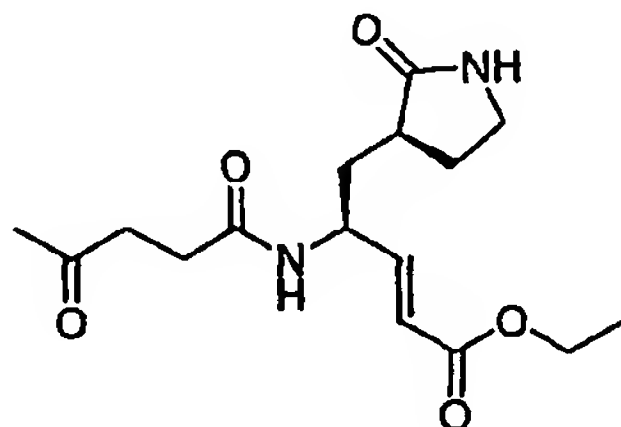
2R-Benzyl-N,N-dimethyl-succinamic acid (prepared according to the procedure described in Example 8, starting with hydrocinnamic acid) was reacted with 2-(2-trifluoromethyl-phenyl)-1H-pyrrole (prepared according to the procedure described in Example 6), then demethylated to give 2R-benzyl-4-oxo-4-[5-(2-trifluoromethyl-phenyl)-1H-pyrrol-2-yl]-butyric acid (all following Method 8), then coupled to Gln-resin, following Method 1. ¹H NMR (CD₃OD) δ 7.70 (1H, d, J = 7.3), 7.58-7.41 (3H, m), 7.25-7.11 (5H, m), 6.95 (1H, d, J = 4.0), 6.53 (1H, dd, J = 15.8, 5.1), 6.35 (1H, d, J = 3.9) 5.38 (1H, dd, J = 15.8, 1.7), 4.47-4.38 (1H, m), 4.12 (2H, q, J = 7.1), 3.31 (1H, m), 3.08-2.70 (4H, m), 2.13 (2H, t, J = 7.9), 1.92-1.78 (1H, m), 1.63-1.50 (1H, m), 1.25 (3H, t, J = 7.1). HRMS (MALDI) 606.2194 (MNa⁺, calcd. 606.2192).

15

EXAMPLE 42

4S-(4-oxo-pentanoylamino)-5-(2-oxo-pyrrolidin-3S-yl)-pent-2-enoic acid ethyl ester (Compound 43)

20



4S-Amino-5-(2-oxo-pyrrolidin-3S-yl)-pent-2-enoic acid ethyl ester (0.15 mmol, 35 mg) in DMF (1.5 ml) was treated with diisopropylethyl amine (0.30 mmol, 0.05 ml), 4-oxopentanoic acid (0.15 mmol, 27 mg), and HATU (0.15 mmol, 57 mg), and held at

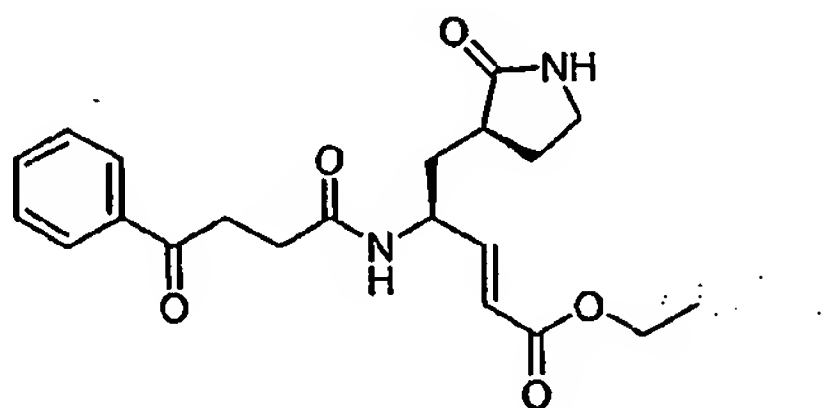
- 135 -

room temperature for 1 h. The solution was washed with brine (10 ml), and extracted with EtOAc (2x10 ml) and concentrated under reduced pressure to provide 40 mg of crude product. Purification by preparative reverse phase chromatography (CH₃CN-H₂O) provided 28 mg (48%) of the title product. ¹H NMR (CDCl₃) δ 7.28 (1H, s), 6.83 (1H, dd, J = 15.7, 5.2), 6.03 (1H, s), 5.92 (1H, dd, J = 15.7, 1.5), 4.65-4.50 (1H, m), 4.17 (2H, q, J = 7.1), 3.40-3.30 (2H, m), 2.92-2.65 (2H, m), 2.60-2.35 (4H, m), 2.17 (3H, m), 2.05-1.90 (1H, m), 1.90-1.72 (1H, m), 1.70-1.60 (1H, m), 1.27 (3H, t, J = 7.1). MS (ES) 347 (MNa⁺), 323 (M-H)⁻.

10

EXAMPLE 43

4S-(4-oxo-4-phenyl-butyrylamino)-5-(2-oxo-pyrrolidin-3S-yl)-pent-2-enoic acid ethyl ester. (Compound 44)



15

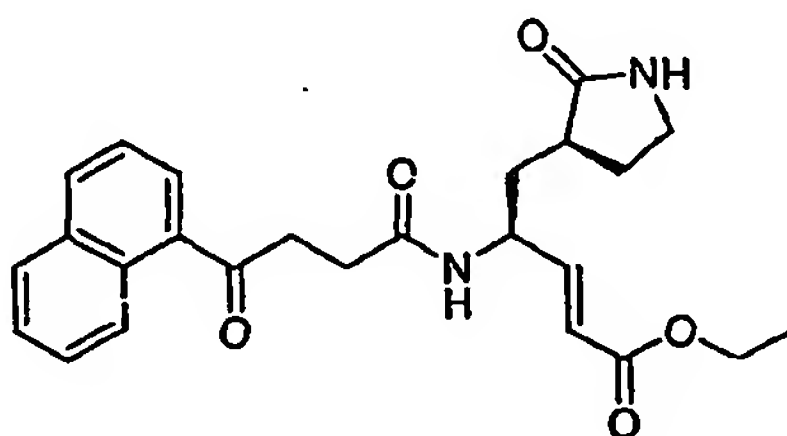
The title compound was prepared according to the method of Example 42, using 4-oxo-4-phenylbutyric acid. ¹H NMR (CDCl₃) δ 8.10-7.95 (2H, m), 7.60-7.53 (1H, m), 7.50-7.42 (2H, m), 6.86 (1H, dd, J = 15.6, 5.7), 5.97 (1H, d, J = 15.6), 5.73 (1H, s), 4.65-4.61 (1H, m), 4.19 (2H, q, J = 7.1), 3.50-3.20 (4H, m), 2.73-2.64 (2H, m), 2.62-2.35 (2H, m), 2.08-1.95 (1H, m), 1.92-1.65 (2H, m), 1.28 (3H, t, J = 7.1). MS (ES) 387 (MH⁺), 409 (MNa⁺).

20

EXAMPLE 44

4-S-(4-Naphthalen-1-yl-4-oxo-butyrylamino)-5-(2-oxo-pyrrolidin-3S-yl)-pent-2-enoic acid ethyl ester. (Compound 45)

25

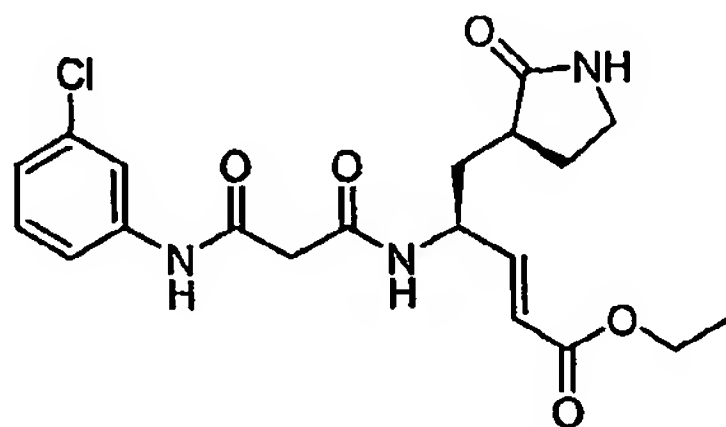


- 136 -

The title compound was prepared according to the method of Example 42, using as starting material gamma-oxo-1-naphthalene butyric acid. ¹H NMR (CDCl₃) δ 8.57 (1H, d, J = 8.6), 7.99-7.37 (7H, m), 6.88 (1H, dd, J = 15.6, 5.4), 6.05 (1H, s), 6.01 (1H, d, J = 15.6), 4.65-4.64 (1H, m), 4.17 (2H, q, J = 7.2), 3.57-3.27 (4H, m), 2.86-2.39 (4H, m), 2.09-1.66 (3H, m), 1.25 (3H, t, J = 7.2). MS (FAB) 437.2068 (MH⁺, calcd. 437.2076).

EXAMPLE 45

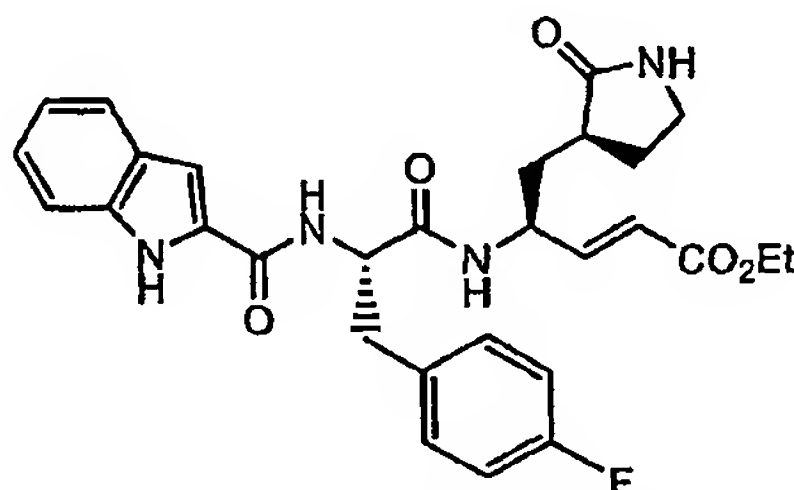
4S-[2-(3-Chloro-phenylcarbamoyl)-acetylamino]-5-(2-oxo-pyrrolidin-3S-yl)-pent-2-enoic acid ethyl ester. (Compound 46)



The title compound was prepared according to the method of Example 42, using as starting material N-(3-chloro-phenyl)-malonamic acid. ¹H NMR (CDCl₃) δ 9.89 (1H, s), 8.69 (1H, d, J = 6.1), 7.69 (1H, s), 7.41-7.36 (1H, m), 7.22 (1H, t, J = 8.1), 7.09-7.03 (1H, m), 6.84 (1H, dd, J = 15.7, 5.7), 5.96 (1H, d, J = 15.6), 5.97 (1H, s), 4.59-4.48 (1H, m), 4.18 (2H, q, J = 7.1), 3.43-3.34 (4H, m), 2.57-2.37 (2H, m), 2.06-1.80 (2H, m), 1.74 (1H, dt, J = 14.5, 4.3), 1.27 (3H, t, J = 7.1). MS (FAB) 422.1494 (MH⁺, calcd 422.1483), 444 (MNa⁺).

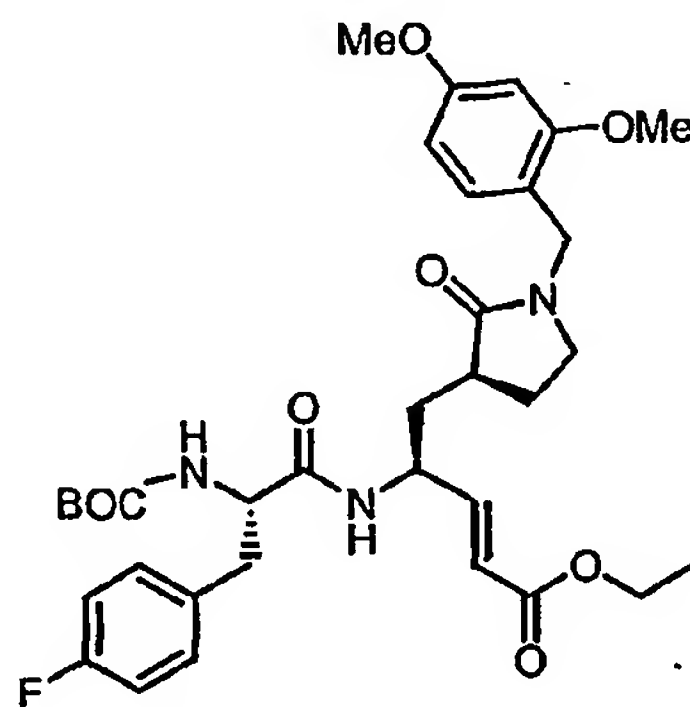
EXAMPLE 46

Preparation of Ethyl-3-{(Indole-2-carboxylic acid)-L-(4-F-Phe)-L-[(S)-Pyrrol-Ala]}-E-Propenoate. (Compound 42)



5 In this example, the following shorthand naming system employing amino acid abbreviations is used to identify some intermediates and final products. When naming compounds, italicized amino acid abbreviations represent modifications at the C-terminus of that residue where the following apply: (1) acrylic acid esters are reported as "E" (trans) propenoates; (2) substituted 3-methylene-dihydrofuran-2-ones are reported as "E" (trans) 2-(a-vinyl-g-butyrolactones); and (3) 5-vinylisoxazoles are reported as "E" (trans) propenisoxazoles.

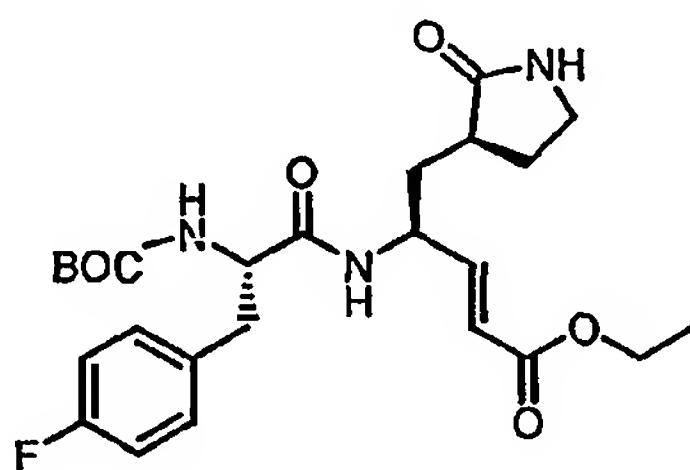
Ethyl-3-{Boc-L-(4-F-Phe)-L-[(N-2,4-Dimethoxybenzyl)-(S)-Pyrrol-Ala]}-E-Propenoate



15 A solution of HCl in 1,4-dioxane (4.0 M, 12 ml) was added to a solution of ethyl-3-{Boc-L-[(N-2,4-dimethoxybenzyl)-(S)-Pyrrol-Ala]}-E-propenoate, prepared according to the procedure described in Dragovich, et al., *J. Med. Chem.* 1999, 42, 1213, (0.432 g, 0.906 mmol, 1 equiv) in the same solvent (12 ml). After stirring 1.5 h at 23 °C, the solvent was concentrated under reduced pressure to give the crude amine salt. This material was dissolved in DMF (7 ml) and cooled to 0 °C. Boc-L-(4-F-Phe)-OH

(0.308 g, 1.09 mmol, 1.2 equiv), N,N-diisopropylethylamine (0.474 ml, 2.72 mmol, 3 equiv) and HATU (0.379 g, 0.997 mmol, 1.1 equiv) were added sequentially and the reaction mixture was allowed to warm to 23 °C. After 1.5 h, the mixture was diluted with MTBE (200 ml), and washed with 5% KHSO₄ and brine (20 ml each), dried over
 5 MgSO₄ and concentrated. The residue was purified by flash column chromatography (60% EtOAc in hexanes) to provide ethyl-3-{Boc-L-(4-F-Phe)-L-[(N-2,4-dimethoxybenzyl)-(S)-Pyrrol-Ala]}-E-propenoate (0.447 g, 77%) as a white foam: R_f = 0.34 (60% EtOAc in hexanes); IR (cm⁻¹) 3258, 1705, 1666; ¹H NMR (CDCl₃) δ 1.28 (t, 3H, J = 7.2), 1.45 (s, 9H), 1.51-1.66 (m, 2H), 1.78-1.90 (m, 1H), 2.06-2.23 (m, 2H),
 10 2.99 (dd, 1H, J = 13.7, 6.2), 3.11 (dd, 1H, J = 13.7, 5.3), 3.17-3.23 (m, 2H), 3.80 (s, 3H), 3.81 (s, 3H), 4.18 (q, 2H, J = 7.2), 4.35 (s, 2H), 4.38-4.51 (m, 2H), 5.29-5.37 (m, 1H), 5.76 (d, 1H, J = 15.8), 6.43-6.47 (m, 2H), 6.72 (dd, 1H, J = 15.8, 5.3), 6.83-6.91 (m, 2H), 7.09-7.17 (m, 3H), 7.92 (br, 1H); Anal. (C₃₄H₄₄FN₃O₈) C, H, N.

15 Preparation of Intermediate Ethyl-3-{Boc-L-(4-F-Phe)-L-[(S)-Pyrrol-Ala]}-E-Propenoate



2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (0.14 g, 0.62 mmol, 1 equiv) was
 20 added to a solution of ethyl-3-{Boc-L-(4-F-Phe)-L-[(N-2,4-dimethoxybenzyl)-(S)-pyrrol-Ala]}-E-propenoate (0.39 g, 0.53 mmol, 1 equiv) in CHCl₃ (25 ml) and water (2.5 ml) and the reaction mixture was heated to reflux at 60 °C. After 2 h, an additional equivalent of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone was added to the mixture. After 2 h, one more equivalent of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone was
 25 added to the mixture. The reaction mixture was diluted with EtOAc (150 ml) and washed sequentially with NaHCO₃ (100 ml) and brine (100 ml). The organic layers were dried over Na₂SO₄, concentrated, and the residue was purified by flash column chromatography (2% CH₃OH in CH₂Cl₂) to afford ethyl-3-{Boc-L-(4-F-Phe)-L-[(S)-pyrrol-Ala]}-E-propenoate (0.205 g, 79%) as a white solid: R_f = 0.18 (5%

- 139 -

CH₃OH in CH₂Cl₂); IR (cm⁻¹) 3281, 2981, 1690; ¹H NMR (CDCl₃) δ 1.27-1.31 (t, 3H, J = 7.2), 1.42 (s, 9H), 1.57-1.64 (m, 1H), 1.75-1.94 (m, 2H), 2.23-2.36 (m, 2H), 3.01-3.05 (m, 2H), 3.29-3.34 (m, 2H), 4.18 (q, 2H, J = 7.2), 4.42-4.50 (m, 2H), 5.23 (m, 1H), 5.69-5.79 (m, 2H), 6.69-6.74 (m, 1H), 6.94-7.00 (m, 1H), 7.14-7.18 (m, 2H), 7.43 (m, 1H); Anal. Calcd for C₂₅H₃₄FN₃O₆·0.5H₂O C, 59.99; H, 7.05; N, 8.39. Found C, 59.63; H, 7.05; N, 8.14.

Ethyl-3-{(Indole-2-carboxylic acid)-L-(4-F-Phe)-L-[(S)-Pyrrol-Ala]}-E-Propenoate

A solution of HCl in 1,4-dioxane (4.0 M, 2 ml) was added to ethyl-3-{Boc-L-(4-F-Phe)-L-[(S)-pyrrol-Ala]}-E-propenoate (0.19 g, 0.39 mmol, 1 equiv) in 2 ml of 1,4-dioxane at 23 °C. After 2 h, the volatiles were removed under reduced pressure and CH₂Cl₂ (3 ml) and Et₃N (1 ml) were added sequentially to the residue. In a separate flask, N-hydroxysuccinimide (0.075 g, 0.65 mmol, 1.1 equiv) and 1,3-dicyclohexylcarbodiimide (0.13 g, 0.64 mmol, 1.1 equiv) were added to a solution of indole-2-carboxylic acid (0.99 g, 0.62 mmol, 1 equiv) in CH₂Cl₂ (3 ml) and DMF (1 ml) and stirred at 23 °C for 3 h. This solution was then filtered and added to the original reaction mixture described above. The resulting solution was stirred at 23 °C for 16 h. then was partitioned between water (25 ml) and CH₂Cl₂ (2 x 20 ml). The combined organic layers were dried over Na₂SO₄, concentrated, and the residue was purified by flash column chromatography (1 to 5 % CH₃OH in CH₂Cl₂) to afford ethyl-3-{(indole-2-carboxylic acid)-L-(4-F-Phe)-L-[(S)-pyrrol-Ala]}-E-propenoate (0.145 g, 70%) as a white powder: R_f = 0.44 (10% CH₃OH in CH₂Cl₂); IR (cm⁻¹) 3277, 1636, 1547; ¹H NMR (DMSO-d₆) δ 1.28 (t, 3H, J = 7.2), 1.51-1.59 (m, 1H), 1.66-1.73 (m, 1H), 1.89-1.96 (m, 1H), 2.10-2.18 (m, 1H), 2.39-2.42 (m, 1H), 3.09-3.17 (m, 4H), 4.18 (q, 2H, J = 7.5), 4.62 (m, 1H), 4.75-4.77 (m, 1H), 5.71-5.82 (m, 1H), 6.87 (dd, 1H, J = 4.2, 15.9), 7.07-7.17 (m, 3H), 7.21-7.26 (m, 3H), 7.42-7.47 (m, 3H), 7.66-7.70 (m, 2H), 8.45 (d, 1H, J = 8.7), 8.72 (d, 1H, J = 7.8); Anal. Calcd for C₂₉H₃₁FN₄O₅·0.35 H₂O: C, 64.40; H, 5.91; N, 10.36. Found C, 64.12; H, 5.91; N, 10.14.

Results of tests conducted using exemplary compounds of the invention are described below.

BIOCHEMICAL AND BIOLOGICAL EVALUATION

Inhibition of Rhinovirus 3C Protease:

Stock solutions (50 mM, in DMSO) of various compounds were prepared; dilutions were in the same solvent. Recombinant rhinovirus 3C proteases (see Birch et al., "Purification of recombinant human rhinovirus 14 3C protease expressed in *Escherichia coli*," *Protein Expr. Pur.* (1995), vol. 6(5), 609-618) from serotypes 14, 16, and 2 were prepared by the following standard chromatographic procedures: (1) ion exchange using Q Sepharose Fast Flow from Pharmacia; (2) affinity chromatography using Affi-Gel Blue from Biorad; and (3) sizing using Sephadex G-100 from Pharmacia. Each assay sample contained 2% DMSO, 50 mM tris pH 7.6, 1 mM EDTA, a test compound at the indicated concentration, approximately 1 μ M substrate, and 50-100 nM protease. The k_{obs}/I values were obtained from reactions initiated by addition of enzyme rather than substrate. RVP activity was measured in the fluorescence resonance energy transfer assay. The substrate was (N-terminal) DABCYL-(Gly-Arg-Ala-Val-Phe-Gln-Gly-Pro-Val-Gly)-EDANS. In the uncleaved peptide, the EDANS fluorescence was quenched by the proximal DABCYL moiety. When the peptide was cleaved, the quenching was relieved, and activity was measured as an increase in fluorescence signal. Data were analyzed using standard non-linear fitting programs (Enzfit), and are shown in the table below. The tabulated data in the column designated $k_{obs}/[I]$ were measured from progress curves in enzyme start experiments.

Antirhinoviral H1-HeLa Cell Culture Assay:

In this cell protection assay, the ability of compounds to protect cells against HRV infection was measured by the XTT dye reduction method, which is described in Weislow et al., *J. Natl. Cancer Inst.* (1989), vol. 81, 577-586. H1-HeLa cells were infected with HRV-14 at a multiplicity of infection (m.o.i.) of 0.13 (virus particles/cell) or mock-infected with medium only. Infected or mock-infected cells were resuspended at 8×10^5 cells per ml, and incubated with appropriate concentrations of the compounds to be tested. Two days later, XTT/PMS was added to test plates and the amount of formazan produced was quantified spectrophotometrically at 450/650 nm.

The EC₅₀ value was calculated as the concentration of compound that increased the percentage of formazan production in compound-treated, virus-infected cells to 50% of that produced by compound-free, mock-infected cells. The 50% cytotoxic dose (CC₅₀) was calculated as the concentration of compound that decreased the percentage of formazan produced in compound-treated, mock-infected cells to 50% of that produced by compound-free, mock-infected cells. The therapeutic index (TI) was calculated by dividing the CC₅₀ value by the EC₅₀ value.

All strains of human rhinovirus (HRV) for use in this assay were purchased from American Type Culture Collection (ATCC), except for HRV serotype-14 (produced from the infectious cDNA clone constructed by Dr. Robert Rueckert, Institute for Molecular Virology, University of Wisconsin, Madison, Wisconsin). HRV stocks were propagated and viral assays were performed in H1-HeLa cells (ATCC). Cells were grown in minimal essential medium with 10% fetal bovine serum, available from Life Technologies (Gaithersburg, MD). Test results for the HRV assay are shown in the table below.

Anticoxsackieviral Cell Culture Assay:

Coxsackievirus types A-21 (CAV-21) and B3 (CVB3) were purchased from American Type Culture Collection (ATCC, Rockville, MD). Virus stocks were propagated and antiviral assays were performed in H1-HeLa cells (ATCC). Cells were grown in minimal essential medium with 10% fetal bovine serum (Life Technologies, Gaithersburg, MD). The ability of the compounds of this invention to protect cells against either CAV-21 or CVB3 infection was measured by the XTT dye reduction method. This method is described in Weislow et al., J. Natl. Cancer Inst. (1989), vol. 81, 577-586. H1-HeLa cells were infected with CAV-21 or CVB3 at a multiplicity of infection (m.o.i.) of 0.025 or 0.075, respectively, or mock-infected with medium only. H1-HeLa cells were plated at 4×10^4 cells per well in a 96-well plate and incubated with appropriate concentrations of the test compound. One day (CVB3) or two days (CAV-21) later, XTT/PMS was added to test plates and the amount of formazan produced was quantified spectrophotometrically at 450/650 nm. The EC₅₀ was calculated as the concentration of compound that increased the formazan production in compound-treated, virus-infected cells to 50% of that produced by compound-free,

uninfected cells. The 50% cytotoxic dose (CC₅₀) was calculated as the concentration of compound that decreased formazan production in compound-treated, uninfected cells to 50% of that produced in compound-free, uninfected cells. The therapeutic index (TI) was calculated by dividing the CC₅₀ by the EC₅₀.

5

Anti-Echoviral and Anti-Enteroviral Cell Culture Assays:

Echovirus type 11 (ECHO 11) was purchased from ATCC (Rockville, MD). Virus stocks were propagated and antiviral assays were performed in MRC-5 cells (ATCC). Cells were grown in minimal essential medium with 10% fetal bovine serum (Life Technologies, Gaithersburg, MD). The ability of the compounds of this invention to protect cells against ECHO 11 infection was measured by the XTT dye reduction method (Weislow et al., J. Natl. Cancer Inst. (1989), vol. 81, 577-586). MRC-5 cells were infected with ECHO 11 at an m.o.i. of 0.003 or 0.004, respectively, or mock-infected with medium only. Infected or uninfected cells were added at 1×10^4 cells per well and incubated with appropriate concentrations of compound. Four days later, XTT/PMS was added to test plates, and the amount of formazan produced was quantified spectrophotometrically at 450/650 nm. The EC₅₀ was calculated as the concentration of compound that increased the formazan production in compound-treated, virus-infected cells to 50% of that produced by compound-free, uninfected cells. The 50% cytotoxic dose (CC₅₀) was calculated as the concentration of compound that decreased formazan production in compound-treated, uninfected cells to 50% of that produced in compound-free, uninfected cells. The therapeutic index (TI) was calculated by dividing the CC₅₀ by the EC₅₀. Activity of the compounds against enterovirus type 70 (EV 70) may be measured by the same assay as described above in this section. Enterovirus type 70 (EV 70) may be obtained from the American Type Culture Collection ATCC (Rockville, MD).

30

Antiviral data obtained for the test compounds are shown in the table below. The designation "ND" indicates that a value was not determined for that compound, and the designation "NA" means not applicable.

TABLE

	Compound #	Virus Serotype	K_{obs}/I ($M^{-1}s^{-1}$)	EC ₅₀ (μM)	CC ₅₀ (μM)
5	1	HRV-14	20300	0.202	>10
	2	HRV-14	32400	0.064	>10
	3	HRV-14	30800	0.109	>10
	4	HRV-14	5860	ND	ND
	5	HRV-14	12700	1.098	>10
10	6	HRV-14	2130	1.425	>10
	7	HRV-14	5200	0.3	>10
	8	HRV-14	1300	4.924	>10
	9	HRV-14	12550	ND	ND
	10	HRV-14	2370	ND	ND
15	11	HRV-14	5000	0.646	>10
	12	HRV-14	2700	1.248	>10
	13	HRV-14	6570	2.01	>10
	14	HRV-14	34600	0.534	>10
	15	HRV-14	980	27.0	>100
20	16	HRV-14	7100	1.321	>10
	17	HRV-14	2900	2.186	>10
	18	HRV-14	3140	1.597	>10
	19	HRV-14	6650	1.527	>10
	20	HRV-14	330	16.42	>100
25	21	HRV-14	1380	ND	ND
	22	HRV-14	4400	5.719	>10
	23	HRV-14	3800	1.546	>10
	24	HRV-14	5460	3.914	>100
	25	HRV-14	690000	0.034	>10
30		HRV-1A	ND	0.089	>10
		HRV-10	ND	0.148	>10
		CAV-21	ND	0.2	>10
		ECHO-11	ND	0.044	>10
		ENT-70	ND	.003	>10
35	26	HRV-14	188000	0.073	>10
	27	HRV-14	11700	1.585	>10
	28	HRV-14	340000	0.059	>1
		HRV-1A	ND	0.213	>1
		HRV-10	ND	0.066	>1
40	29	HRV-14	103000	0.15	>10
		HRV-1A	ND	0.054	>10
		HRV-10	ND	0.027	>10
		HRV-3	ND	0.065	>10
		HRV-25	ND	0.316	>10
45		HRV-9	ND	0.119	>10
		HRV-39	ND	0.180	>10
	30	HRV-14	2500	3.336	>10
	31	HRV-14	900	ND	ND

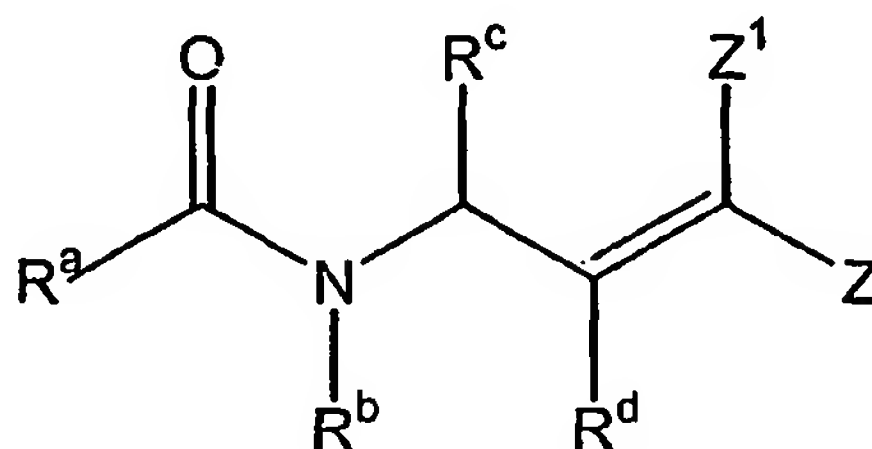
- 144 -

	Compound #	Virus Serotype	K_{obs}/I ($M^{-1}s^{-1}$)	EC ₅₀ (μM)	CC ₅₀ (μM)
5	32	HRV-14	8300	ND	ND
	33	HRV-14	100000	0.212	>10
	34	HRV-14	520	ND	ND
	35	HRV-14	125000	0.143	>10
	36	HRV-14	59300	0.17	>10
10		HRV-1A	ND	0.145	>10
		HRV-10	ND	0.330	>10
		HRV-3	ND	0.145	>10
		HRV-25	ND	0.329	>10
		HRV-9	ND	0.144	>10
15		HRV-39	ND	0.235	>10
		HRV-14	27900	0.541	>10
	37	HRV-14	26400	0.266	>10
	38	HRV-1A	ND	0.537	>10
		HRV-10	ND	0.446	>10
20		HRV-39	ND	0.593	>10
		HRV-87	ND	0.097	>10
		HRV-2	ND	0.353	>10
		HRV-3	ND	0.605	>10
		HRV-9	ND	0.885	>10
25		HRV-16	ND	1.49	>10
		HRV-25	ND	1.51	>10
		HRV-14	33000	0.136	>10
	39	HRV-1A	ND	0.338	>10
		HRV-10	ND	0.428	>10
30		HRV-39	ND	0.518	>10
		HRV-87	ND	0.083	>10
		HRV-2	ND	0.214	>10
		HRV-3	ND	0.595	>10
		HRV-9	ND	0.665	>10
35		HRV-16	ND	0.952	>10
		HRV-25	ND	1.32	>10
		HRV-14	20100	0.214	>10
	40	HRV-14	3175	1.656	>10
	41	HRV-14	10700	0.50	>10
40	42	HRV-14	42	ND	ND
	43	HRV-14	85	ND	ND
	44	HRV-14	1031	ND	ND
	45	HRV-14	629	ND	ND
	46				

While the invention has been described in terms of preferred embodiments and specific examples, those skilled in the art will recognize through routine experimentation that various changes and modifications can be made without departing from the spirit and scope of the invention. Thus, the invention should be understood as not being limited
5 by the foregoing detailed description, but as being defined by the appended claims and their equivalents. .

WE CLAIM:

1. An antipicornaviral compound having the formula:



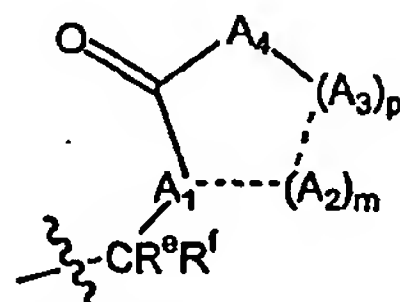
wherein:

R^a is an alkylcarbonylalkyl, cycloalkylcarbonylalkyl, arylcarbonylalkyl, heteroarylcarbonylalkyl, alkylcarbonylaminoalkyl, cycloalkylcarbonylaminoalkyl, heterocycloalkylcarbonylaminoalkyl, arylcarbonylaminoalkyl, heteroarylcarbonylaminoalkyl, alkylaminocarbonylalkyl, cycloalkylaminocarbonylalkyl, heterocycloalkylaminocarbonylalkyl, arylaminocarbonylalkyl, heteroarylaminocarbonylalkyl group, where each alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl moiety thereof may be unsubstituted or substituted with one or more suitable substituents;

R^b is H or an alkyl group, unsubstituted or substituted with one or more suitable substituents;

R^d is H, halo, hydroxyl, or an alkyl, alkoxy or alkylthio group, where the alkyl, alkoxy or alkylthio group is unsubstituted or substituted with one or more suitable substituents;

R^c is a moiety having the formula:



R^e and R^f are each independently H or a lower alkyl group;

m is 0 or 1, provided that when m is 1, R^a is not an amino-substituted alkylcarbonylalkyl or amino-substituted alkylcarbonylaminoalkyl group, and when m is 0, R^a is selected from an alkylaminocarbonylalkyl, cycloalkylaminocarbonylalkyl, heterocycloalkylaminocarbonylalkyl, arylaminocarbonylalkyl,

heteroarylaminoacylalkyl and heteroarylcarbonylaminoalkyl group, provided that R^a is not substituted indolecarbonylaminoalkyl;

p is an integer of from 0 to 5;

A_1 is CH or N;

when p is 1, 2, 3, 4, or 5, A_2 is $C(R^g)(R^h)$, $N(R^i)$, S, $S(O)$, $S(O)_2$, or O, and when p is 0, A_2 is $C(R^g)(R^h)(R^i)$, $N(R^g)(R^i)$, $S(R^g)$, $S(O)(R^g)$, $S(O)_2(R^g)$, or $O(R^g)$, where each R^g , R^h and R^i is independently H or a lower alkyl group;

each A_3 present is independently $C(R^g)(R^h)$, $N(R^i)$, S, $S(O)$, $S(O)_2$, or O, where each R^g , R^h and R^i is independently H or a lower alkyl group;

when p is 1, 2, 3, 4, or 5, A_4 is $N(R^j)$, $C(R^g)(R^h)$, or O, and when p is 0, A_4 is $N(R^j)(R^h)$, $C(R^g)(R^h)(R^i)$, and $O(R^h)$, where each R^g , R^h and R^i is independently H or a lower alkyl group, each R^j is H, an alkyl, aryl, or acyl group, and each R^k is H or an alkyl or aryl group;

provided that no more than two heteroatoms occur consecutively in the above-depicted ring formed by A_1 , $(A_2)_m$, $(A_3)_p$, A_4 , and $C=O$, where each dotted line in the ring depicts a single bond when A_2 is present and a hydrogen atom when A_2 is absent; and

Z and Z^1 are each independently H, F, an alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group, where the alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group is unsubstituted or substituted with one or more suitable substituents, $-C(O)R^l$, $-CO_2R^l$, $-CN$, $-C(O)NR^lR^m$, $-C(O)NR^lOR^m$, $-C(S)R^l$, $-C(S)OR^l$, $-C(S)NR^lR^m$, $-C(=NR^l)R^m$, $-C(=NR^l)OR^m$, $-NO_2$, $-SOR^m$, $-SO_2R^l$, $-SO_2NR^lR^m$, $-SO_2(NR^l)(OR^m)$, $-SONR^l$, $-SO_3R^l$, $-PO(OR^l)_2$, $-PO(OR^l)(OR^m)$, $-PO(NR^lR^m)(OR^l)$, $-PO(NR^lR^m)(NR^lR^o)$, $-C(O)NR^lNR^mR^n$, $-C(S)NR^lNR^mR^n$, where R^l , R^m , R^n and R^o are each independently H or an alkyl, cycloalkyl, aryl, heterocycloalkyl, acyl or thioacyl group, where the alkyl, cycloalkyl, aryl, heterocycloalkyl, acyl or thioacyl group is unsubstituted or substituted with one or more suitable substituents, or where any two of the R^l , R^m , R^n and R^o , taken together with the atoms to which they are bonded, form a heterocycloalkyl group, which may be optionally substituted,

or Z and R^d , together with the atoms to which they are bonded, form a cycloalkyl or heterocycloalkyl group, where Z and R^d are as defined above except for moieties that cannot form the cycloalkyl or heterocycloalkyl group,

- 148 -

or Z and Z¹, together with the atoms to which they are bonded, form a cycloalkyl or heterocycloalkyl group, where Z and Z¹ are as defined above;

or a prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate of said compound.

2. The compound according to claim 1, wherein

A₁ is CH or N;

A₂ is C(R^g)(R^h), N(Rⁱ), S, S(O), S(O)₂, or O, where each R^g, R^h and Rⁱ is independently H or a lower alkyl group;

each A₃ present is independently C(R^g)(R^h), N(Rⁱ), S, S(O), S(O)₂, or O, where each R^g, R^h and Rⁱ is independently H or a lower alkyl group;

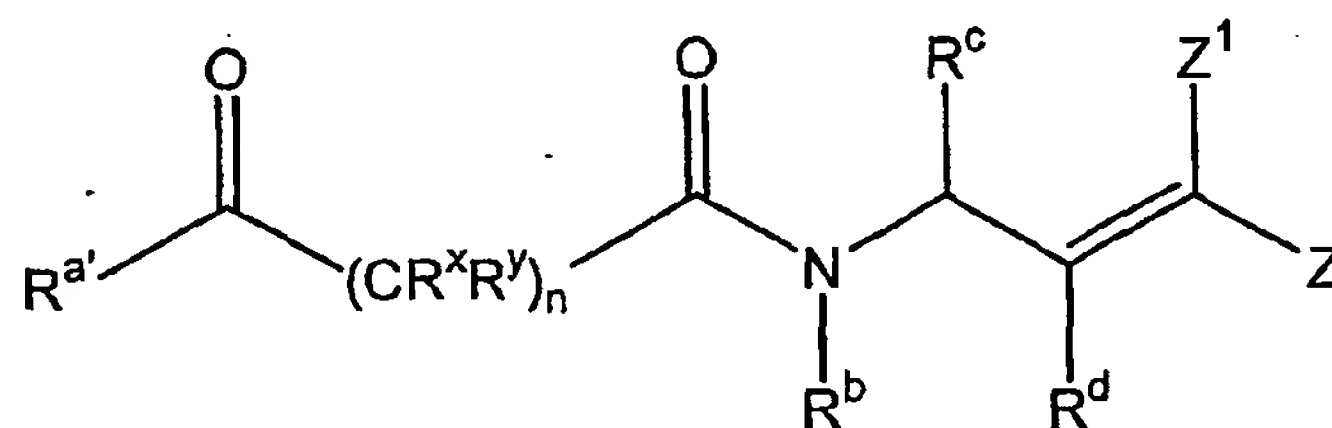
when p is 1, 2, 3, 4, or 5, A₄ is N(R^j), C(R^g)(R^h), or O, and when p is 0, A₄ is N(R^j)(R^k), C(R^g)(R^h)(Rⁱ), and O(R^k), where each R^g, R^h and Rⁱ is independently H or a lower alkyl group, each R^j is H, an alkyl, aryl, or acyl group, and each R^k is H or an alkyl or aryl group;

provided that no more than two heteroatoms occur consecutively in the above-depicted ring formed by A₁, (A₂)_m, (A₃)_p, A₄, and C=O, where each dotted line in the ring depicts a single bond when A₂ is present and a hydrogen atom when A₂ is absent; and

Z and Z¹ are each independently H, F, an alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group, where the alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group is unsubstituted or substituted with one or more suitable substituents, -C(O)R¹, -CO₂R¹, -CN, -C(O)NR¹R^m, -C(O)NR¹OR^m, -C(S)R¹, -C(S)NR¹R^m, -NO₂, -SOR^m, -SO₂R¹, -SO₂NR¹R^m, -SO₂(NR¹)(OR^m), -SONR¹, -SO₃R¹, -PO(OR¹)₂, -PO(OR¹)(OR^m), -PO(NR¹R^m)(ORⁿ), -PO(NR¹R^m)(NRⁿR^o), -C(O)NR¹NR^mRⁿ, -C(S)NR¹NR^mRⁿ, where R¹, R^m, Rⁿ and R^o are each independently H, an alkyl, cycloalkyl, aryl, heterocycloalkyl, acyl or thioacyl group, where the alkyl, cycloalkyl, aryl, heterocycloalkyl, acyl or thioacyl group is unsubstituted or substituted with one or more suitable substituents, or where any two of the R¹, R^m, Rⁿ and R^o, taken together with the atoms to which they are bonded, form a heterocycloalkyl group, which is unsubstituted or substituted with one or more suitable substituents, or Z and Z¹,

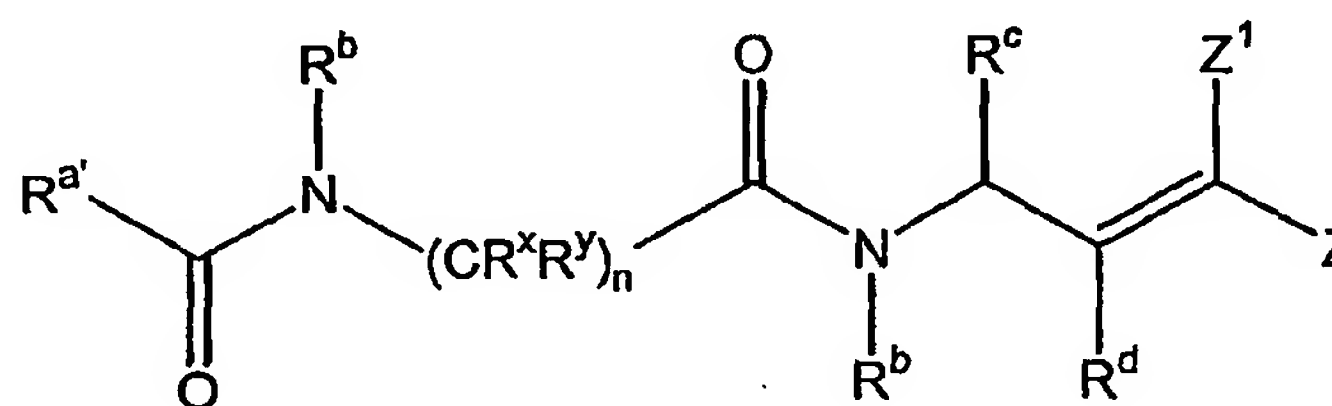
together with the atoms to which they are bonded, form a cycloalkyl or heterocycloalkyl group, where Z and Z¹ are as defined above.

3. The compound according to claim 1 or 2, having the formula:



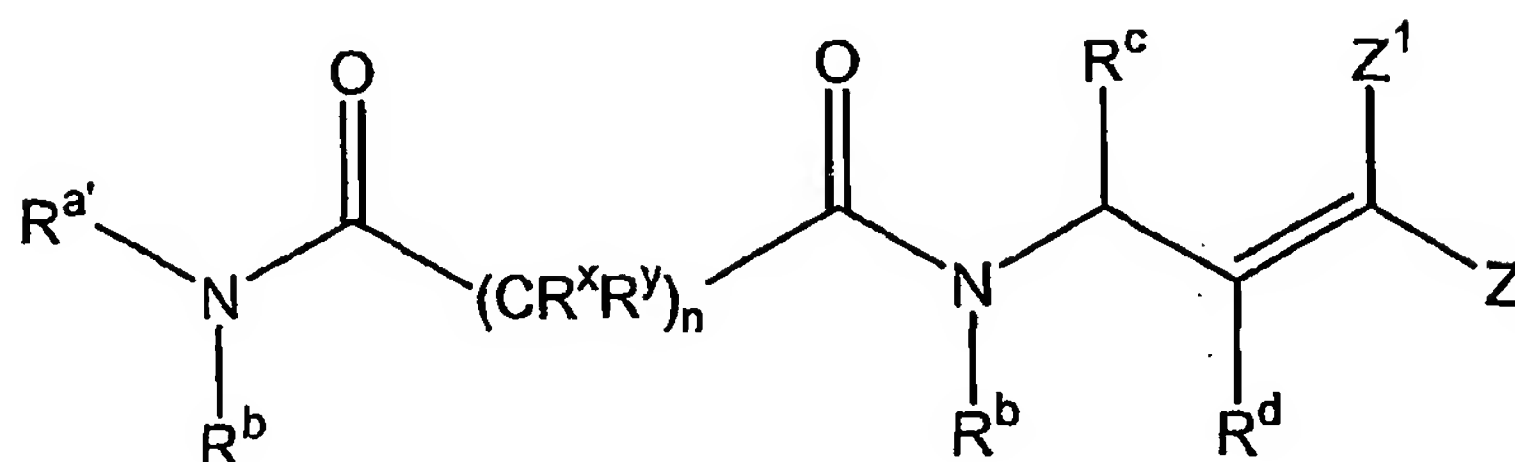
wherein R^{a'} is an alkyl, cycloalkyl, aryl or heteroaryl group, where said alkyl, cycloalkyl, aryl or heteroaryl group is unsubstituted or substituted with one or more suitable substituents, n is 1, 2 or 3, m is 1, R^x and R^y are each independently selected from H and an alkyl group, unsubstituted or substituted with one or more suitable substituents, and R^b, R^c, R^d, Z and Z¹ are as defined in claim 1 or 2, respectively, provided that R^{a'} is not an amino-substituted alkyl group.

4. The compound according to claim 1 or 2, having the formula:



wherein R^{a'} is an alkyl, cycloalkyl, aryl or heteroaryl group, where said alkyl, cycloalkyl, aryl or heteroaryl group is unsubstituted or substituted with one or more suitable substituents, n is 1, 2 or 3, m is 1, R^x and R^y are each independently selected from H and an alkyl group, unsubstituted or substituted with one or more suitable substituents, and R^b, R^c, R^d, Z and Z¹ are as defined in claim 1 or 2, respectively, provided that R^{a'} is not an amino-substituted alkyl group.

5. The compound according to claim 1 or 2, having the formula:



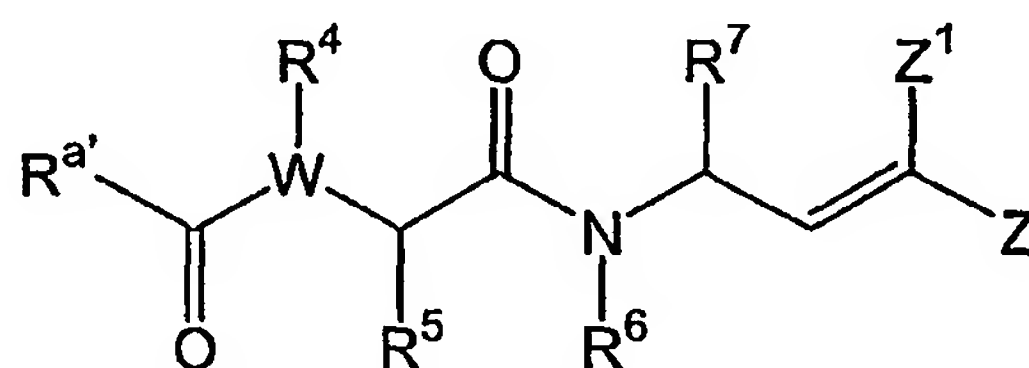
wherein R^{a} is an alkyl, aryl, cycloalkyl, heterocycloalkyl or heteroaryl group, where said alkyl, aryl, cycloalkyl, heterocycloalkyl and heteroaryl group is unsubstituted or substituted with one or more suitable substituents, n is 1, 2 or 3, R^{x} and R^{y} are each independently selected from H and an alkyl group, unsubstituted or substituted with one or more suitable substituents, and R^{b} , R^{c} , R^{d} , Z and Z^1 are as defined as in claim 1 or 2, respectively.

6. The compound according to claim 1 or 2, wherein said substituted alkyl, aryl, cycloalkyl, heterocycloalkyl or heteroaryl comprises one or more substituents independently selected from an alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, nitro, amino, cyano, halo, hydroxyl, alkoxy, alkylendioxy, aryloxy, cycloalkoxy, heterocycloalkoxy, heteroaryloxy, alkylcarbonyl, alkyloxycarbonyl, alkylcarbonyloxy, arylcarbonyl, arylcarbonyloxy, aryloxycarbonyl, cycloalkylcarbonyl, cycloalkylcarbonyloxy, cycloalkyloxycarbonyl, heteroarylcarbonyl, heteroarylcarbonyloxy, heteroaryloxycarbonyl, heterocycloalkylcarbonyl, heterocycloalkylcarbonyloxy, heterocycloalkyloxycarbonyl, carboxyl, carbamoyl, formyl, keto, thioketo, sulfo, alkylamino, cycloalkylamino, arylamino, heterocycloalkylamino, heteroarylamino, dialkylamino, alkylaminocarbonyl, cycloalkylaminocarbonyl, arylaminocarbonyl, heterocycloalkylaminocarbonyl, heteroarylaminocarbonyl, dialkylaminocarbonyl, alkylaminothiocarbonyl, cycloalkylaminothiocarbonyl, arylaminothiocarbonyl, heterocycloalkylaminothiocarbonyl, heteroarylaminothiocarbonyl, dialkylaminothiocarbonyl, alkylsulfonyl, arylsulfonyl, alkylsulfenyl, arylsulfenyl, alkylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino,

heterocycloalkylcarbonylamino, heteroarylcarbonylamino, alkylthiocarbonylamino, cycloalkylthiocarbonylamino, arylthiocarbonylamino, heterocycloalkylthiocarbonylamino, heteroarylthiocarbonylamino, alkylsulfonyloxy, arylsulfonyloxy, alkylsulfonylamino, arylsulfonylamino, mercapto, alkylthio, arylthio and heteroarylthio group, where any of the alkyl, alkylene, aryl, cycloalkyl, heterocycloalkyl, heteroaryl moieties present in the above substituents may be further substituted with one or more suitable substituents.

7. The compound according to claim 6, wherein said substituted alkyl, alkylene, aryl, cycloalkyl, heterocycloalkyl, heteroaryl moieties may be further substituted with one or more substituents selected from nitro, amino, cyano, halo, haloalkyl, haloaryl, hydroxyl, keto, hydroxamino, alkylamino, dialkylamino, mercapto, and unsubstituted alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, alkoxy, aryloxy, alkylthio or arylthio groups and wherein any of the aryl or heteroaryl moieties may be substituted with alkylenedioxy.

8. An antipicomaviral compound having the formula:



wherein:

W is CH or N;

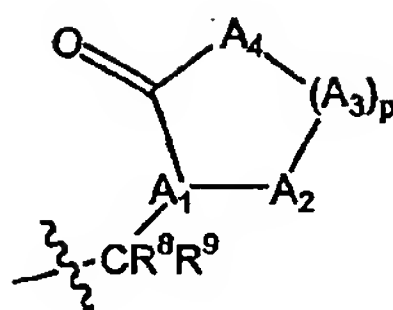
R^{a'} is an alkyl, cycloalkyl, aryl or heteroaryl group, where said alkyl, cycloalkyl, aryl, and heteroaryl group is unsubstituted or substituted with one or more suitable substituents, provided that R^{a'} is not an amino-substituted alkyl group;

R⁴ and R⁶ are each independently H or a lower alkyl group;

R⁵ is H or an alkyl group;

R⁷ is a moiety having the formula:

- 152 -



wherein:

R^8 and R^9 are each independently H or lower alkyl;

p is an integer of from 1 to 5;

A_1 is CH or N;

when p is 1, 2, 3, 4, or 5, A_2 is $C(R^{10})(R^{11})$, $N(R^{12})$, S, $S(O)$, $S(O)_2$, or O, and

when p is 0, A_2 is $C(R^{10})(R^{11})(R^{12})$, $N(R^{10})(R^{12})$, $S(R^{10})$, $S(O)(R^{10})$, $S(O)_2(R^{10})$, or $O(R^{10})$

where each R^{10} , R^{11} and R^{12} is independently H or a lower alkyl group;

each A_3 present is independently $C(R^{10})(R^{11})$, $N(R^{12})$, S, $S(O)$, $S(O)_2$, or O,

where each R^{10} , R^{11} and R^{12} is independently H or a lower alkyl group;

when p is 1, 2, 3, 4, or 5, A_4 is $N(R^{13})$, $C(R^{10})(R^{11})$, or O, and when p is 0, A_4 is $N(R^{13})(R^{14})$, $C(R^{10})(R^{11})(R^{12})$, and $O(R^{14})$, where each R^{10} , R^{11} and R^{12} is independently H or a lower alkyl group, each R^{13} is H or an alkyl, aryl, or acyl group, and each R^{14} is H or an alkyl or aryl group;

provided that no more than two heteroatoms occur consecutively in the above-depicted ring formed by A_1 , $(A_2)_m$, $(A_3)_p$, A_4 , and $C=O$, where each dotted line in the ring depicts a single bond when A_2 is present and a hydrogen atom when A_2 is absent; and

Z and Z^1 are each independently H, F, an alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group, where the alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group is unsubstituted or substituted with one or more suitable substituents, $-C(O)R^{15}$, $-CO_2R^{15}$, $-CN$, $-C(O)NR^{15}R^{16}$, $-C(O)NR^{15}OR^{16}$, $-C(S)R^{15}$, $-C(S)OR^{15}$, $-C(S)NR^{15}R^{16}$, $-C(=NR^{15})R^{16}$, $-C(=NR^{15})OR^{16}$, $-NO_2$, $-SOR^{16}$, $-SO_2R^{15}$, $-SO_2NR^{15}R^{16}$, $-SO_2(NR^{15})(OR^{16})$, $-SONR^{15}$, $-SO_3R^{15}$, $-PO(OR^{15})_2$, $-PO(OR^{15})(OR^{16})$, $-PO(NR^{15}R^{16})(OR^{17})$, $-PO(NR^{15}R^{16})(NR^{17}R^{18})$, $-C(O)NR^{15}NR^{16}R^{17}$, $-C(S)NR^{15}NR^{16}R^{17}$, where R^{15} , R^{16} , R^{17} and R^{18} are each independently H or an alkyl, cycloalkyl, aryl, heterocycloalkyl, acyl or thioacyl group, where the alkyl, cycloalkyl, aryl, heterocycloalkyl, acyl or thioacyl group is unsubstituted or substituted with one or more suitable substituents, or where any two of the R^{15} , R^{16} , R^{17} and R^{18} , taken together with

- 153 -

the atoms to which they are bonded, form a heterocycloalkyl group, which is unsubstituted or substituted with one or more suitable substituents,

or Z and Z¹, together with the atoms to which they are bonded, form a cycloalkyl or heterocycloalkyl group, where Z and Z¹ are as defined above;

or a prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate of said compound.

9. The compound according to claim 8, wherein:

A₁ is CH or N;

A₂ is C(R¹⁰)(R¹¹), N(R¹²), S, S(O), S(O)₂, or O, where each R¹⁰, R¹¹ and R¹² is independently H or a lower alkyl group;

each A₃ present is independently C(R¹⁰)(R¹¹), N(R¹²), S, S(O), S(O)₂, or O, where each R¹⁰, R¹¹ and R¹² is independently H or a lower alkyl group;

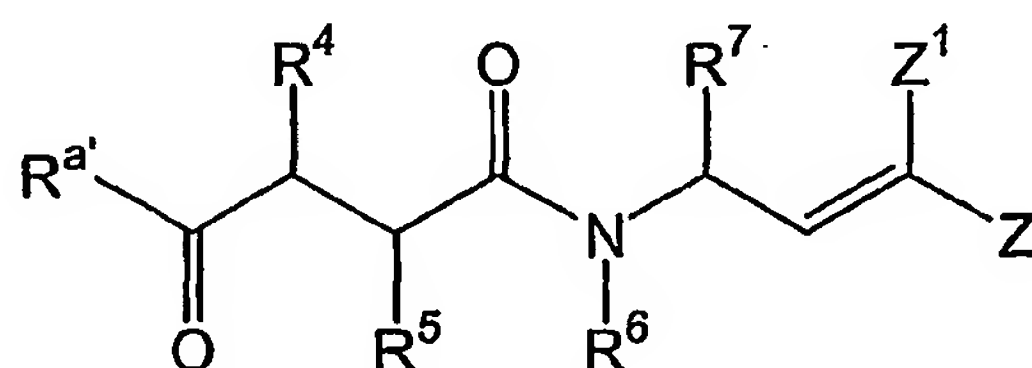
when p is 1, 2, 3, 4, or 5, A₄ is N(R¹³), C(R¹⁰)(R¹¹), or O, and when p is 0, A₄ is N(R¹³)(R¹⁴), C(R¹⁰)(R¹¹)(R¹²), and O(R¹⁴), where each R¹⁰, R¹¹ and R¹² is independently H or a lower alkyl group, each R¹³ is H or an alkyl, aryl, or acyl group, and each R¹⁴ is H or an alkyl or aryl group;

provided that no more than two heteroatoms occur consecutively in the above-depicted ring formed by A₁, (A₂)_m, (A₃)_p, A₄, and C=O, where each dotted line in the ring depicts a single bond when A₂ is present and a hydrogen atom when A₂ is absent; and

Z and Z¹ are each independently H, F, an alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group, where the alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group is unsubstituted or substituted with one or more suitable substituents, -C(O)R¹⁵, -CO₂R¹⁵, -CN, -C(O)NR¹⁵R¹⁶, -C(O)NR¹⁵OR¹⁶, -C(S)R¹⁵, -C(S)NR¹⁵R¹⁶, -NO₂, -SOR¹⁶, -SO₂R¹⁵, -SO₂NR¹⁵R¹⁶, -SO₂(NR¹⁵)(OR¹⁶), -SONR¹⁵, -SO₃R¹⁵, -PO(OR¹⁵)₂, -PO(OR¹⁵)(OR¹⁶), -PO(NR¹⁵R¹⁶)(OR¹⁷), -PO(NR¹⁵R¹⁶)(NR¹⁷R¹⁸), -C(O)NR¹⁵NR¹⁶R¹⁷, -C(S)NR¹⁵NR¹⁶R¹⁷, where R¹⁵, R¹⁶, R¹⁷ and R¹⁸ are each independently H or an alkyl, cycloalkyl, aryl, heterocycloalkyl, acyl or thioacyl group, where the alkyl, cycloalkyl, aryl, heterocycloalkyl, acyl or thioacyl group is unsubstituted or substituted with one or more suitable substituents, or where any two of the R¹⁵, R¹⁶, R¹⁷ and R¹⁸, taken together with the atoms to which they are bonded, form

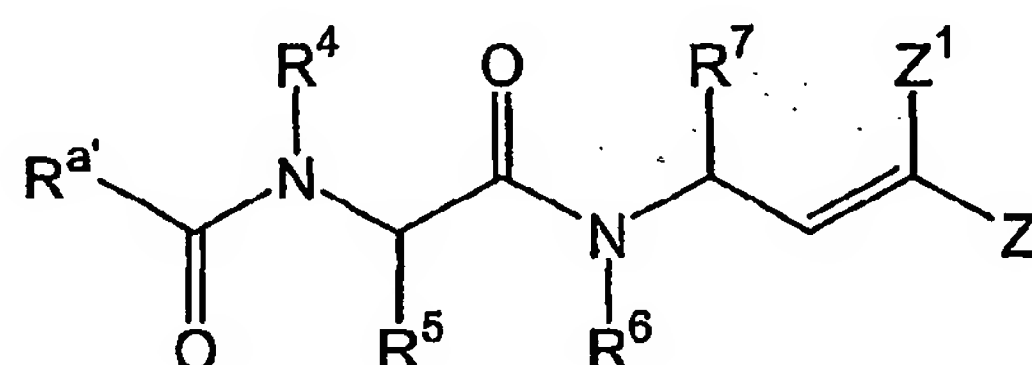
a heterocycloalkyl group, which is unsubstituted or substituted with one or more suitable substituents, or Z and Z¹, together with the atoms to which they are bonded, form a cycloalkyl or heterocycloalkyl group, where Z and Z¹ are as defined above.

10. The compound according to claim 8 or 9, having the formula:



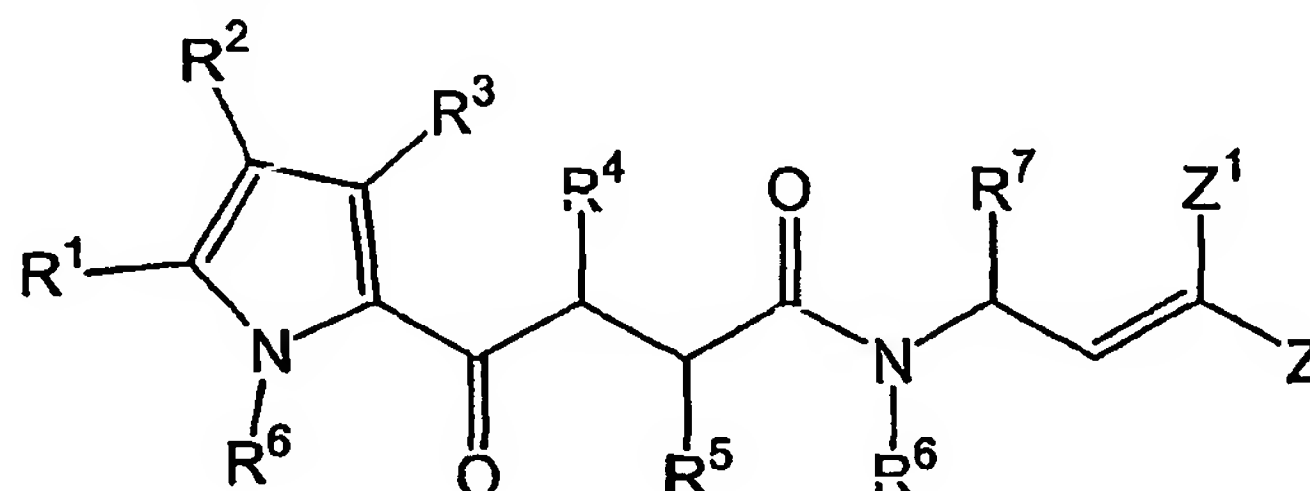
wherein R^{a'} is an alkyl, cycloalkyl, aryl or heteroaryl group, where said alkyl, cycloalkyl, aryl, and heteroaryl group is unsubstituted or substituted with one or more suitable substituents, and R⁴, R⁵, R⁶, R⁷, Z and Z¹ are defined as in claim 8 or 9, respectively, provided that R^{a'} is not amino-substituted alkyl.

11. The compound according to claim 8 or 9, having the formula:



wherein R^{a'} is an alkyl, cycloalkyl, aryl or heteroaryl group, where said alkyl, cycloalkyl, aryl, and heteroaryl group is unsubstituted or substituted with one or more suitable substituents, and R⁴, R⁵, R⁶, R⁷, Z and Z¹ are defined as in claims 8 or 9, respectively, provided that R^{a'} is not amino-substituted alkyl.

12. An antipicornaviral compound having the formula:



wherein:

R^1 is H, halo or an alkoxy, alkyl, aryl, cycloalkyl, heterocycloalkyl or heteroaryl group, where the alkoxy, alkyl, cycloalkyl, heterocycloalkyl or heteroaryl group is unsubstituted or substituted with one or more suitable substituents;

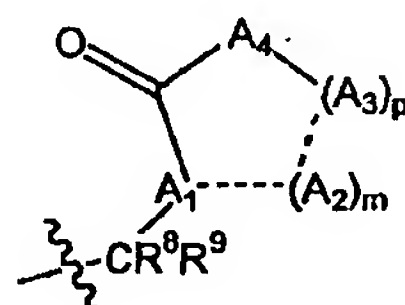
R^2 and R^3 are each independently H, halo or an alkoxy or lower alkyl group, where the alkoxy or lower alkyl group is unsubstituted or substituted with one or more suitable substituents;

or R^1 together with R^2 form a cycloalkyl, heterocycloalkyl, aryl or heteroaryl ring, where the cycloalkyl, heterocycloalkyl, aryl or heteroaryl ring is unsubstituted or substituted with one or more suitable substituents;

R^4 and R^6 are each independently H or a lower alkyl group, unsubstituted or substituted with one or more suitable substituents;

R^5 is H or an alkyl group, unsubstituted or substituted with one or more suitable substituents;

R^7 is a moiety having the formula:



wherein:

R^8 and R^9 are each independently H or a lower alkyl group;

m is 0 or 1;

p is an integer of from 0 to 5;

A_1 is CH or N;

when p is 1, 2, 3, 4, or 5, A_2 is $C(R^{10})(R^{11})$, $N(R^{12})$, S, $S(O)$, $S(O)_2$, or O, and

when p is 0, A_2 is $C(R^{10})(R^{11})(R^{12})$, $N(R^{10})(R^{12})$, $S(R^{10})$, $S(O)(R^{10})$, $S(O)_2(R^{10})$, or $O(R^{10})$

where each R^{10} , R^{11} and R^{12} is independently H or a lower alkyl group;

each A_3 present is independently $C(R^{10})(R^{11})$, $N(R^{12})$, S, $S(O)$, $S(O)_2$, or O,

where each R^{10} , R^{11} and R^{12} is independently H or a lower alkyl group;

when p is 1, 2, 3, 4, or 5, A_4 is $N(R^{13})$, $C(R^{10})(R^{11})$, or O, and when p is 0, A_4 is $N(R^{13})(R^{14})$, $C(R^{10})(R^{11})(R^{12})$, and $O(R^{14})$, where each R^{10} , R^{11} and R^{12} is each

- 156 -

independently H or a lower alkyl group, each R^{13} is H or an alkyl, aryl, or acyl group, and each R^{14} is H or an alkyl or aryl group;

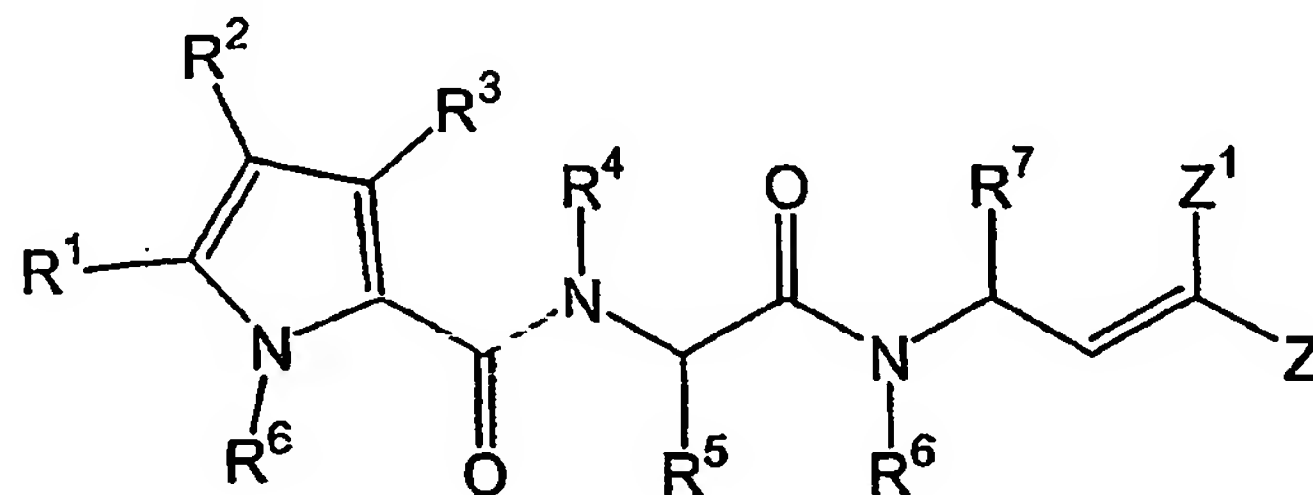
provided that no more than two heteroatoms occur consecutively in the above-depicted ring formed by A_1 , $(A_2)_m$, $(A_3)_p$, A_4 , and $C=O$, where each dotted line in the ring depicts a single bond when A_2 is present and a hydrogen atom when A_2 is absent; and

Z and Z^1 are each independently H, F, an alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group, where the alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group is unsubstituted or substituted with one or more suitable substituents, $-C(O)R^{15}$, $-CO_2R^{15}$, $-CN$, $-C(O)NR^{15}R^{16}$, $-C(O)NR^{15}OR^{16}$, $-C(S)R^{15}$, $-C(S)OR^{15}$, $-C(S)NR^{15}R^{16}$, $-C(=NR^{15})R^{16}$, $-C(=NR^{15})OR^{16}$, $-NO_2$, $-SOR^{16}$, $-SO_2R^{15}$, $-SO_2NR^{15}R^{16}$, $-SO_2(NR^{15})(OR^{16})$, $-SONR^{15}$, $-SO_3R^{15}$, $-PO(OR^{15})_2$, $-PO(OR^{15})(OR^{16})$, $-PO(NR^{15}R^{16})(OR^{17})$, $-PO(NR^{15}R^{16})(NR^{17}R^{18})$, $-C(O)NR^{15}NR^{16}R^{17}$, $-C(S)NR^{15}NR^{16}R^{17}$, where R^{15} , R^{16} , R^{17} and R^{18} are each independently H or an alkyl, cycloalkyl, aryl, heterocycloalkyl, acyl or thioacyl group, where the alkyl, cycloalkyl, aryl, heterocycloalkyl, acyl or thioacyl group is unsubstituted or substituted with one or more suitable substituents, or where any two of the R^{15} , R^{16} , R^{17} and R^{18} , taken together with the atoms to which they are bonded, form a heterocycloalkyl group, which is unsubstituted or substituted with one or more suitable substituents,

or Z and Z^1 , together with the atoms to which they are bonded, form a cycloalkyl or heterocycloalkyl group, where Z and Z^1 are as defined above;

or a prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate thereof of said compound.

13. An antipicornaviral compound having the formula:



wherein:

R^1 is H, halo or an alkoxy, alkyl, aryl, cycloalkyl, heterocycloalkyl, or heteroaryl group, where the alkoxy, alkyl, cycloalkyl, heterocycloalkyl or heteroaryl group is unsubstituted or substituted with one or more suitable substituents;

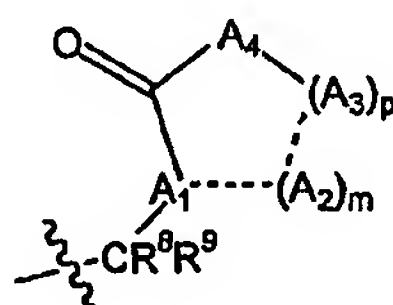
R^2 and R^3 are each independently H, halo or an alkoxy or lower alkyl group, where the alkoxy or lower alkyl group is unsubstituted or substituted with one or more suitable substituents;

or R^1 together with R^2 form a cycloalkyl, heterocycloalkyl, aryl or heteroaryl ring, where the cycloalkyl, heterocycloalkyl, aryl or heteroaryl ring is unsubstituted or substituted with one or more suitable substituents;

R^4 and R^6 are each independently H or a lower alkyl group, unsubstituted or substituted with one or more suitable substituents;

R^5 is H or an alkyl group, unsubstituted or substituted with one or more suitable substituents;

R^7 is a moiety having the formula:



wherein:

R^8 and R^9 are each independently H or a lower alkyl group;

m is 0 or 1, provided that when m is 0 and R^1 together with R^2 form an aryl ring, the aryl ring is unsubstituted;

p is an integer of from 0 to 5;

A_1 is CH or N;

when p is 1, 2, 3, 4, or 5, A_2 is $C(R^{10})(R^{11})$, $N(R^{12})$, S, $S(O)$, $S(O)_2$, or O, and

when p is 0, A_2 is $C(R^{10})(R^{11})(R^{12})$, $N(R^{10})(R^{12})$, $S(R^{10})$, $S(O)(R^{10})$, $S(O)_2(R^{10})$, or $O(R^{10})$

where each R^{10} , R^{11} and R^{12} is independently H or a lower alkyl group;

each A_3 present is independently $C(R^{10})(R^{11})$, $N(R^{12})$, S, $S(O)$, $S(O)_2$, or O,

where each R^{10} , R^{11} and R^{12} is independently H or a lower alkyl group;

when p is 1, 2, 3, 4, or 5, A_4 is $N(R^{13})$, $C(R^{10})(R^{11})$, or O, and when p is 0, A_4 is $N(R^{13})(R^{14})$, $C(R^{10})(R^{11})(R^{12})$, and $O(R^{14})$, where each R^{10} , R^{11} and R^{12} is independently

H or a lower alkyl group, each R^{13} is H or an alkyl, aryl, or acyl group, and each R^{14} is H or an alkyl or aryl group;

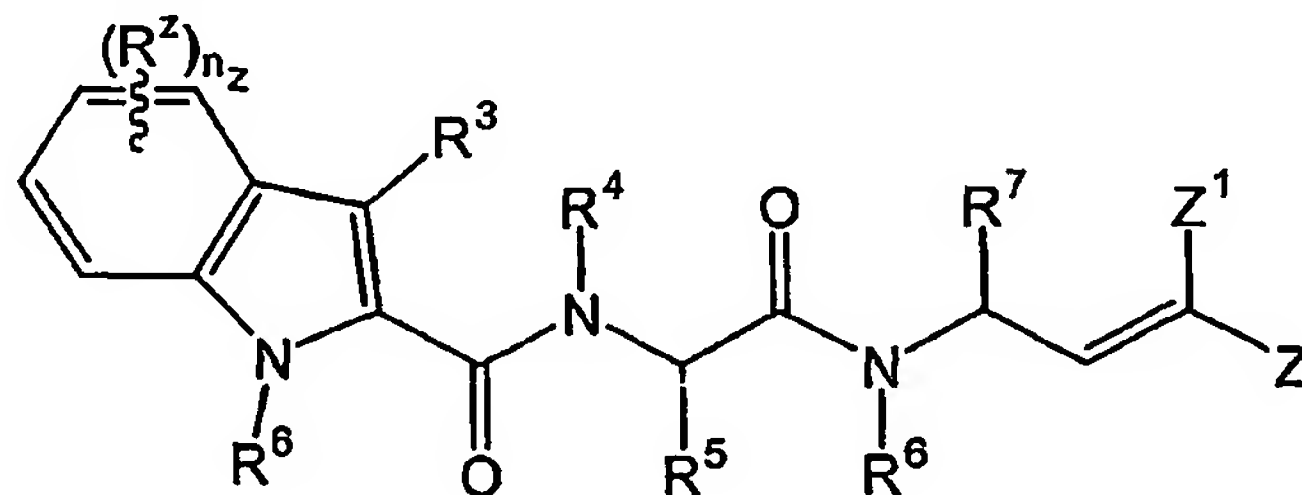
provided that no more than two heteroatoms occur consecutively in the above-depicted ring formed by A_1 , $(A_2)_m$, $(A_3)_p$, A_4 , and $C=O$, where each dotted line in the ring depicts a single bond when A_2 is present and a hydrogen atom when A_2 is absent; and

Z and Z^1 are each independently H, F, an alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group, where the alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group is unsubstituted or substituted with one or more suitable substituents, $-C(O)R^{15}$, $-CO_2R^{15}$, $-CN$, $-C(O)NR^{15}R^{16}$, $-C(O)NR^{15}OR^{16}$, $-C(S)R^{15}$, $-C(S)OR^{15}$, $-C(S)NR^{15}R^{16}$, $-C(=NR^{15})R^{16}$, $-C(=NR^{15})OR^{16}$, $-NO_2$, $-SOR^{16}$, $-SO_2R^{15}$, $-SO_2NR^{15}R^{16}$, $-SO_2(NR^{15})(OR^{16})$, $-SONR^{15}$, $-SO_3R^{15}$, $-PO(OR^{15})_2$, $-PO(OR^{15})(OR^{16})$, $-PO(NR^{15}R^{16})(OR^{17})$, $-PO(NR^{15}R^{16})(NR^{17}R^{18})$, $-C(O)NR^{15}NR^{16}R^{17}$, $-C(S)NR^{15}NR^{16}R^{17}$, where R^{15} , R^{16} , R^{17} and R^{18} are each independently H or an alkyl, cycloalkyl, aryl, heterocycloalkyl, acyl or thioacyl group, where the alkyl, cycloalkyl, aryl, heterocycloalkyl, acyl or thioacyl group is unsubstituted or substituted with one or more suitable substituents, or where any two of the R^{15} , R^{16} , R^{17} and R^{18} , taken together with the atoms to which they are bonded, form a heterocycloalkyl group, which is unsubstituted or substituted with one or more suitable substituents,

or Z and Z^1 , together with the atoms to which they are bonded, form a cycloalkyl or heterocycloalkyl group, where Z and Z^1 are as defined above;

or a prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate of said compound.

14. The compound according to claim 13, having the formula:

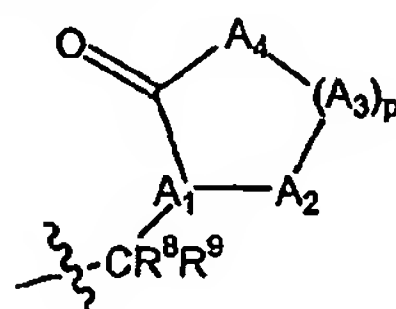


- 159 -

wherein:

each R^z is H or a suitable substituent and n_z is an integer from 1 to 4;

R^7 is a moiety having the formula:



wherein:

R^8 and R^9 are each independently H or a lower alkyl group;

p is an integer of from 1 to 5;

A_1 is CH or N;

when p is 1, 2, 3, 4, or 5, A_2 is $C(R^{10})(R^{11})$, $N(R^{12})$, S, $S(O)$, $S(O)_2$, or O, and

when p is 0, A_2 is $C(R^{10})(R^{11})(R^{12})$, $N(R^{10})(R^{12})$, $S(R^{10})$, $S(O)(R^{10})$, $S(O)_2(R^{10})$, or $O(R^{10})$

where each R^{10} , R^{11} and R^{12} is independently H or a lower alkyl group;

each A_3 present is independently $C(R^{10})(R^{11})$, $N(R^{12})$, S, $S(O)$, $S(O)_2$, or O,

where each R^{10} , R^{11} and R^{12} is independently H or a lower alkyl group;

A_4 is $N(R^{13})$, $C(R^{10})(R^{11})$, or O, where R^{10} and R^{11} are each independently H or a lower alkyl group, and R^{13} is H or an alkyl, aryl or acyl group;

provided that no more than two heteroatoms occur consecutively in the above-depicted ring formed by A_1 , $(A_2)_m$, $(A_3)_p$, A_4 , and $C=O$; and

R^3 , R^4 , R^5 , R^6 , Z and Z^1 are defined as in claim 13.

15. The compound according to claim 14, wherein each R^z is independently selected from H, halo, alkoxy, unsubstituted lower alkyl, haloalkyl, and lower alkoxyalkyl.

16. The compound according to any one of claims 12, 13 or 14, wherein:

A_1 is CH or N;

A_2 is $C(R^{10})(R^{11})$, $N(R^{12})$, S, $S(O)$, $S(O)_2$, or O, where each R^{10} , R^{11} and R^{12} is independently H or a lower alkyl group;

each A_3 present is independently $C(R^{10})(R^{11})$, $N(R^{12})$, S, $S(O)$, $S(O)_2$, or O, where each R^{10} , R^{11} and R^{12} is independently H or a lower alkyl group;

- 160 -

when p is 1, 2, 3, 4, or 5, A_4 is $N(R^{13})$, $C(R^{10})(R^{11})$, or O , and when p is 0, A_4 is $N(R^{13})(R^{14})$, $C(R^{10})(R^{11})(R^{12})$, and $O(R^{14})$, where each R^{10} , R^{11} and R^{12} is independently H or a lower alkyl group, each R^{13} is H or an alkyl, aryl, or acyl group, and each R^{14} is H or an alkyl or aryl group;

provided that no more than two heteroatoms occur consecutively in the above-depicted ring formed by A_1 , $(A_2)_m$, $(A_3)_p$, A_4 , and $C=O$, where each dotted line in the ring depicts a single bond when A_2 is present and a hydrogen atom when A_2 is absent; and

Z and Z^1 are each independently H , F , an alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group, where the alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group is unsubstituted or substituted with one or more suitable substituents, $-C(O)R^{15}$, $-CO_2R^{15}$, $-CN$, $-C(O)NR^{15}R^{16}$, $-C(O)NR^{15}OR^{16}$, $-C(S)R^{15}$, $-C(S)NR^{15}R^{16}$, $-NO_2$, $-SOR^{16}$, $-SO_2R^{15}$, $-SO_2NR^{15}R^{16}$, $-SO_2(NR^{15})(OR^{16})$, $-SONR^{15}$, $-SO_3R^{15}$, $-PO(OR^{15})_2$, $-PO(OR^{15})(OR^{16})$, $-PO(NR^{15}R^{16})(OR^{17})$, $-PO(NR^{15}R^{16})(NR^{17}R^{18})$, $-C(O)NR^{15}NR^{16}R^{17}$, $-C(S)NR^{15}NR^{16}R^{17}$, where R^{15} , R^{16} , R^{17} and R^{18} are each independently H or an alkyl, cycloalkyl, aryl, heterocycloalkyl, acyl or thioacyl group, where the alkyl, cycloalkyl, aryl, heterocycloalkyl, acyl or thioacyl group is unsubstituted or substituted with one or more suitable substituents, or where any two of the R^{15} , R^{16} , R^{17} and R^{18} , taken together with the atoms to which they are bonded, form a heterocycloalkyl group, which is unsubstituted or substituted with one or more suitable substituents, or Z and Z^1 , together with the atoms to which they are bonded, form a cycloalkyl or heterocycloalkyl group, where Z and Z^1 are as defined above.

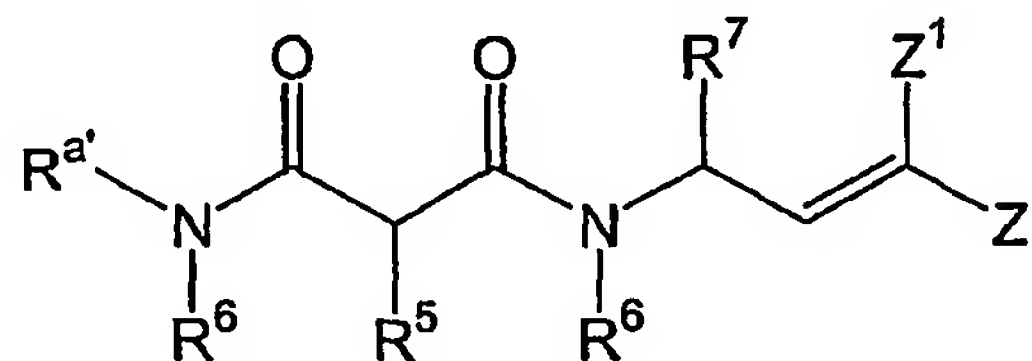
17. The compound according to any one of claims 12, 13 or 14, wherein said substituted alkyl, aryl, cycloalkyl, heterocycloalkyl or heteroaryl comprises one or more substituents independently selected from an alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, nitro, amino, cyano, halo, hydroxyl, alkoxy, alkylendioxy, aryloxy, cycloalkoxy, heterocycloalkoxy, heteroaryloxy, alkylcarbonyl, alkylloxycarbonyl, alkylcarbonyloxy, arylcarbonyl, arylcarbonyloxy, aryloxycarbonyl, cycloalkylcarbonyl, cycloalkylcarbonyloxy, cycloalkyloxycarbonyl, heteroarylcarbonyl, heteroarylcarbonyloxy, heteroaryloxycarbonyl, heterocycloalkylcarbonyl, heterocycloalkylcarbonyloxy, heterocycloalkyloxycarbonyl, carboxyl, carbamoyl,

- 161 -

formyl, keto, thioketo, sulfo, alkylamino, cycloalkylamino, arylamino, heterocycloalkylamino, heteroarylamino, dialkylamino, alkylaminocarbonyl, cycloalkylaminocarbonyl, arylaminocarbonyl, heterocycloalkylaminocarbonyl, heteroarylaminocarbonyl, dialkylaminocarbonyl, alkylaminothiocarbonyl, cycloalkylaminothiocarbonyl, arylaminothiocarbonyl, heterocycloalkylaminothiocarbonyl, heteroarylaminothiocarbonyl, dialkylaminothiocarbonyl, alkylsulfonyl, arylsulfonyl, alkylsulfenyl, arylsulfenyl, alkylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, heterocycloalkylcarbonylamino, heteroarylcarbonylamino, alkylthiocarbonylamino, cycloalkylthiocarbonylamino, arylthiocarbonylamino, heterocycloalkylthiocarbonylamino, heteroarylthiocarbonylamino, alkylsulfonyloxy, arylsulfonyloxy, alkylsulfonylamino, arylsulfonylamino, mercapto, alkylthio, arylthio and heteroarylthio group, where any of the alkyl, alkylene, aryl, cycloalkyl, heterocycloalkyl, heteroaryl moieties present in the above substituents may be further substituted with one or more suitable substituents.

18. The compound according to any one of claims 12, 13 or 14, wherein said substituted alkyl, alkylene, aryl, cycloalkyl, heterocycloalkyl, heteroaryl moieties may be further substituted with one or more suitable substituents selected from nitro, amino, cyano, halo, haloalkyl, haloaryl, hydroxyl, keto, hydroxamino, alkylamino, dialkylamino, mercapto, and unsubstituted alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, alkoxy, aryloxy, alkylthio or arylthio groups and wherein said aryl or heteroaryl moieties may be substituted with alkylenedioxy.

19. An antipicomaviral compound having the formula:



- 162 -

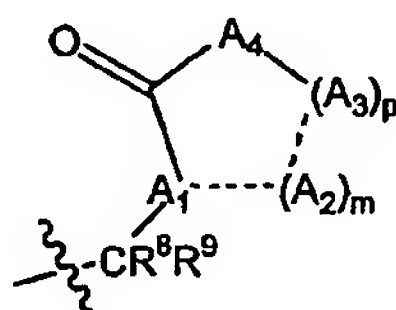
wherein:

R^4 is an alkyl, aryl, cycloalkyl, heterocycloalkyl or heteroaryl, unsubstituted or substituted with one or more suitable substituents,;

R^5 is H or an alkyl group, unsubstituted or substituted with one or more suitable substituents,;

each R^6 is independently H or a lower alkyl group, unsubstituted or substituted with one or more suitable substituents,;

R^7 is a moiety having the formula:



wherein:

R^8 and R^9 are each independently H or a lower alkyl group;

m is 0 or 1;

p is an integer of from 0 to 5;

A_1 is CH or N;

when p is 1, 2, 3, 4, or 5, A_2 is $C(R^{10})(R^{11})$, $N(R^{12})$, S, $S(O)$, $S(O)_2$, or O, and when p is 0, A_2 is $C(R^{10})(R^{11})(R^{12})$, $N(R^{10})(R^{12})$, $S(R^{10})$, $S(O)(R^{10})$, $S(O)_2(R^{10})$, or $O(R^{10})$, where each R^{10} , R^{11} and R^{12} is independently H or a lower alkyl group;

each A_3 present is independently $C(R^{10})(R^{11})$, $N(R^{12})$, S, $S(O)$, $S(O)_2$, or O, where each R^{10} , R^{11} and R^{12} is each independently H or a lower alkyl group;

when p is 1, 2, 3, 4, or 5, A_4 is $N(R^{13})$, $C(R^{10})(R^{11})$, or O, and when p is 0, A_4 is $N(R^{13})(R^{14})$, $C(R^{10})(R^{11})(R^{12})$, and $O(R^{14})$, where each R^{10} , R^{11} and R^{12} is independently H or a lower alkyl group, each R^{13} is H or an alkyl, aryl, or acyl group, and each R^{14} is H or an alkyl or aryl group;

provided that no more than two heteroatoms occur consecutively in the above-depicted ring formed by A_1 , $(A_2)_m$, $(A_3)_p$, A_4 , and $C=O$, where each dotted line in the ring depicts a single bond when A_2 is present and a hydrogen atom when A_2 is absent; and

Z and Z^1 are each independently H, F, an alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group, where the alkyl, cycloalkyl, heterocycloalkyl, aryl or

- 163 -

heteroaryl group is unsubstituted or substituted with one or more suitable substituents, $-C(O)R^{15}$, $-CO_2R^{15}$, $-CN$, $-C(O)NR^{15}R^{16}$, $-C(O)NR^{15}OR^{16}$, $-C(S)R^{15}$, $-C(S)OR^{15}$, $-C(S)NR^{15}R^{16}$, $-C(=NR^{15})R^{16}$, $-C(=NR^{15})OR^{16}$, $-NO_2$, $-SOR^{16}$, $-SO_2R^{15}$, $-SO_2NR^{15}R^{16}$, $-SO_2(NR^{15})(OR^{16})$, $-SONR^{15}$, $-SO_3R^{15}$, $-PO(OR^{15})_2$, $-PO(OR^{15})(OR^{16})$, $-PO(NR^{15}R^{16})(OR^{17})$, $-PO(NR^{15}R^{16})(NR^{17}R^{18})$, $-C(O)NR^{15}NR^{16}R^{17}$, $-C(S)NR^{15}NR^{16}R^{17}$, where R^{15} , R^{16} , R^{17} and R^{18} are each independently H or an alkyl, cycloalkyl, aryl, heterocycloalkyl, acyl or thioacyl group, where the alkyl, cycloalkyl, aryl, heterocycloalkyl, acyl or thioacyl group is unsubstituted or substituted with one or more suitable substituents, or where any two of the R^{15} , R^{16} , R^{17} and R^{18} , taken together with the atoms to which they are bonded, form a heterocycloalkyl group, which is unsubstituted or substituted with one or more suitable substituents,

or Z and Z^1 , together with the atoms to which they are bonded, form a cycloalkyl or heterocycloalkyl group, where Z and Z^1 are as defined above;

or a prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate of said compound.

20. The compound according to claim 19, wherein:

A_1 is CH or N;

A_2 is $C(R^{10})(R^{11})$, $N(R^{12})$, S, S(O), S(O)₂, or O, where each R^{10} , R^{11} and R^{12} is independently H or a lower alkyl group;

each A_3 present is independently $C(R^{10})(R^{11})$, $N(R^{12})$, S, S(O), S(O)₂, or O, where each R^{10} , R^{11} and R^{12} is independently H or a lower alkyl group;

when p is 1, 2, 3, 4, or 5, A_4 is $N(R^{13})$, $C(R^{10})(R^{11})$, or O, and when p is 0, A_4 is $N(R^{13})(R^{14})$, $C(R^{10})(R^{11})(R^{12})$, and $O(R^{14})$, where each R^{10} , R^{11} and R^{12} is independently H or a lower alkyl group, each R^{13} is H or an alkyl, aryl, or acyl group, and each R^{14} is H or an alkyl or aryl group;

provided that no more than two heteroatoms occur consecutively in the above-depicted ring formed by A_1 , $(A_2)_m$, $(A_3)_p$, A_4 , and C=O, where each dotted line in the ring depicts a single bond when A_2 is present and a hydrogen atom when A_2 is absent; and

Z and Z^1 are each independently H, F, an alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group, where the alkyl, cycloalkyl, heterocycloalkyl, aryl or

heteroaryl group is unsubstituted or substituted with one or more suitable substituents, $-C(O)R^{15}$, $-CO_2R^{15}$, $-CN$, $-C(O)NR^{15}R^{16}$, $-C(O)NR^{15}OR^{16}$, $-C(S)R^{15}$, $-C(S)NR^{15}R^{16}$, $-NO_2$, $-SOR^{16}$, $-SO_2R^{15}$, $-SO_2NR^{15}R^{16}$, $-SO_2(NR^{15})(OR^{16})$, $-SONR^{15}$, $-SO_3R^{15}$, $-PO(OR^{15})_2$, $-PO(OR^{15})(OR^{16})$, $-PO(NR^{15}R^{16})(OR^{17})$, $-PO(NR^{15}R^{16})(NR^{17}R^{18})$, $-C(O)NR^{15}NR^{16}R^{17}$, $-C(S)NR^{15}NR^{16}R^{17}$, where R^{15} , R^{16} , R^{17} and R^{18} are each independently H or an alkyl, cycloalkyl, aryl, heterocycloalkyl, acyl or thioacyl group, where the alkyl, cycloalkyl, aryl, heterocycloalkyl, acyl or thioacyl group is unsubstituted or substituted with one or more suitable substituents, or where any two of the R^{15} , R^{16} , R^{17} and R^{18} , taken together with the atoms to which they are bonded, form a heterocycloalkyl group, which is unsubstituted or substituted with one or more suitable substituents, or Z and Z^1 , together with the atoms to which they are bonded, form a cycloalkyl or heterocycloalkyl group, where Z and Z^1 are as defined above.

21. The compound according to any one of claims 8, 9, 12, 13, 14, 19 or 20, wherein R^5 is H or a lower alkyl, arylalkyl, heteroarylalkyl or cycloalkylalkyl group, a straight-chain saturated hydrocarbon moiety or an unsaturated hydrocarbon moiety, where said lower alkyl, arylalkyl, heteroarylalkyl or cycloalkylalkyl group is unsubstituted or substituted with one or more suitable substituents.

22. The compound according to claim 21, wherein R^5 is H or a methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, -methylcyclohexyl, -methylthienyl or benzyl group, unsubstituted or substituted with one or more suitable substituents.

23. The compound according to claim 16, wherein R^5 is H or a methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, -methylcyclohexyl, -methylthienyl or benzyl group, unsubstituted or substituted with one or more suitable substituents.

24. The compound according to claim 21, wherein said substituted methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, -methylcyclohexyl group is substituted by one or

more substituents independently selected from halo, alkoxy, aryloxy, alkylthio and arylthio.

25. The compound according to claim 21, wherein the thienyl moiety of the -methylthienyl group is substituted by one or more substituents independently selected from lower alkyl, lower alkoxy, hydroxy, amino, alkylamino, dialkylamino and halo.

26. The compound according to claim 21, wherein the phenyl moiety of the substituted benzyl is substituted by one or more substituents independently selected from lower alkyl, lower alkoxy, alkylendioxy, hydroxy, amino, alkylamino, dialkylamino and halo.

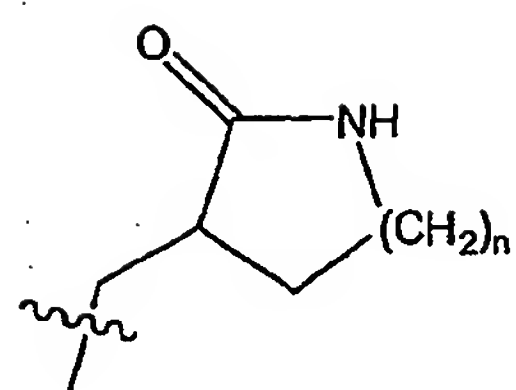
27. The compound according to any one of claims 8, 9, 12, 13, 14, 19 or 20, wherein R^5 is H, ethyl, 2-propyn-1-yl, methylcyclohexyl, or substituted or unsubstituted benzyl, where the phenyl moiety of the substituted benzyl comprises one or more substituents independently selected from lower alkyl, lower alkoxy and halo.

28. The compound according to claim 16, wherein R^5 is H, ethyl, 2-propyn-1-yl, methylcyclohexyl, or substituted or unsubstituted benzyl, where the phenyl moiety of the substituted benzyl comprises one or more substituents independently selected from lower alkyl, lower alkoxy and halo.

29. The compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable salt according to any one of claims 8, 9, 12, 13, 14, 19 or 20, where m is 0 and p is 0 or m is 1 and p is 1 or 2.

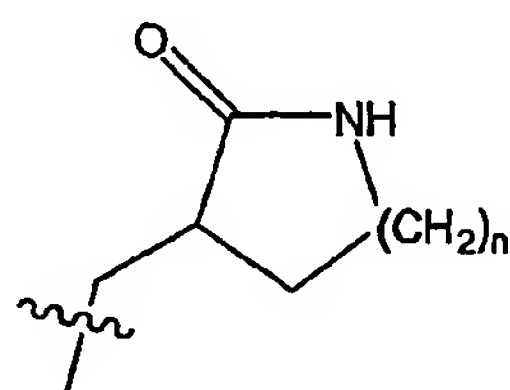
30. The compound according to any one of claims 8, 9, 12, 13, 14, 19 or 20,, wherein R^7 is selected from $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$; $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH-alkyl}$; $-\text{CH}_2\text{NHC}(\text{O})\text{CH}_3$; and

- 166 -



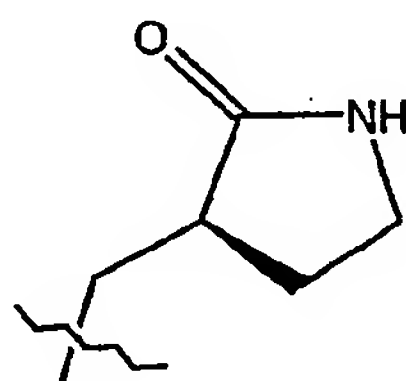
, where n is 1 or 2.

31. The compound according to claim 16, wherein R^7 is selected from $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$; $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH-alkyl}$; $-\text{CH}_2\text{NHC}(\text{O})\text{CH}_3$; and



, where n is 1 or 2.

32. The compound according to any one of claims 8, 9, 12, 13, 14, 19 or 20, wherein R^7 is



33. The compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to any one of claims 8, 12, 13 or 19, wherein Z and Z^1 are each independently selected from H, alkyl, where the alkyl is unsubstituted or substituted with one or more suitable substituents, and $-\text{CO}_2\text{R}^{15}$ or taken together with the atom to which they are attached, form a heterocycloalkyl group, which is optionally substituted with one or more suitable substituents.

34. The compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to claim 9, wherein Z and Z^1 are each independently selected from H, lower alkyl which is unsubstituted or substituted with one or more suitable substituents, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{-alkyl}$ and $-\text{CO}_2\text{-cycloalkyl}$, or taken together with the atom to which they are attached form a

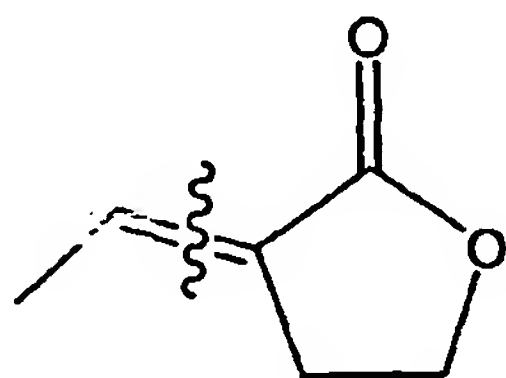
heterocycloalkyl group, which is optionally substituted with one or more of keto or thioketo.

35. The compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to claim 16, wherein Z and Z¹ are each independently selected from H, lower alkyl which is unsubstituted or substituted with one or more suitable substituents, -CO₂H, -CO₂-alkyl and -CO₂-cycloalkyl, or taken together with the atom to which they are attached form a heterocycloalkyl group, which is optionally substituted with one or more of keto or thioketo.

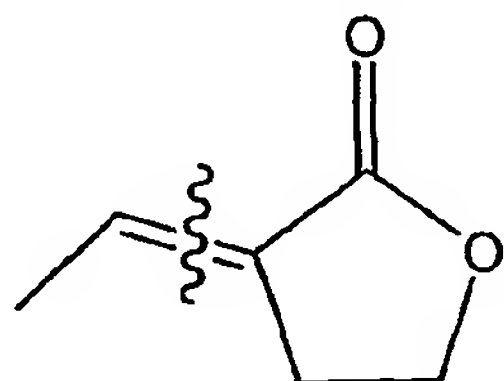
36. The compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to claim 20, wherein Z and Z¹ are each independently selected from H, lower alkyl which is unsubstituted or substituted with one or more suitable substituents, -CO₂H, -CO₂-alkyl and -CO₂-cycloalkyl, or taken together with the atom to which they are attached form a heterocycloalkyl group, which is optionally substituted with one or more of keto or thioketo.

37. The compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to any one of claims 8, 12, 13 or 19, wherein Z and Z¹ are not both H.

38. The compound according to claim 9, wherein Z¹ is H and Z is -CO₂CH₂CH₃, -CO₂(CH(CH₃)₂), -CO₂(C(CH₃)₃), -CO₂CH₂(C(CH₃)₃), -CO₂(cyclo-C₅H₉) or Z¹ and Z taken together with the atom to which they are attached form

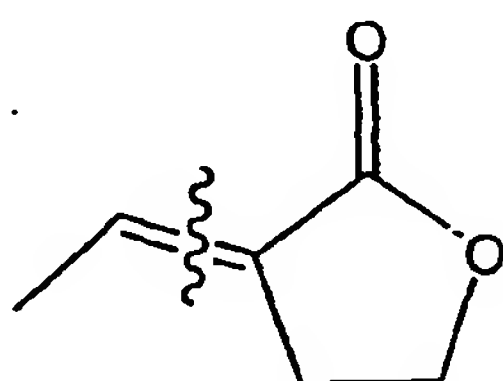


39. The compound according to claim 16, wherein Z^1 is H and Z is $-\text{CO}_2\text{CH}_2\text{CH}_3$, $-\text{CO}_2(\text{CH}(\text{CH}_3)_2)$, $-\text{CO}_2(\text{C}(\text{CH}_3)_3)$, $-\text{CO}_2\text{CH}_2(\text{C}(\text{CH}_3)_3)$, $-\text{CO}_2(\text{cyclo-C}_5\text{H}_9)$ or Z^1 and Z taken together with the atom to which they are attached form

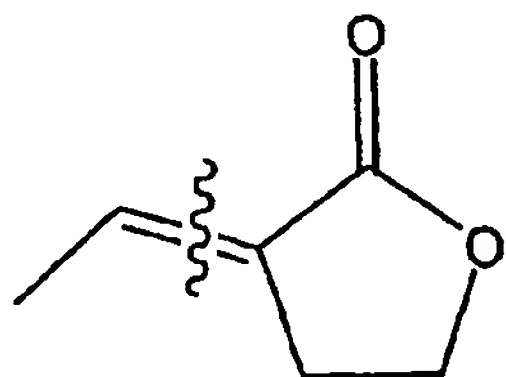


40. The compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according to any one of claims 1, 8, 12, 13 or 19, wherein Z^1 is H or a lower alkyl and Z is $-\text{CO}_2\text{H}$, $-\text{CO}_2$ -alkyl, $-\text{CO}_2$ -alkylaryl, $-\text{CO}_2$ -alkylheteroaryl, $-\text{CO}_2$ -cycloalkyl group, where the lower alkyl, -alkyl, -cycloalkyl, -alkylaryl, -alkylheteroaryl moieties thereof are unsubstituted or substituted with one or more suitable substituents, or Z^1 and Z taken together with the atom to which they are attached form a heterocycloalkyl group, which is optionally substituted.

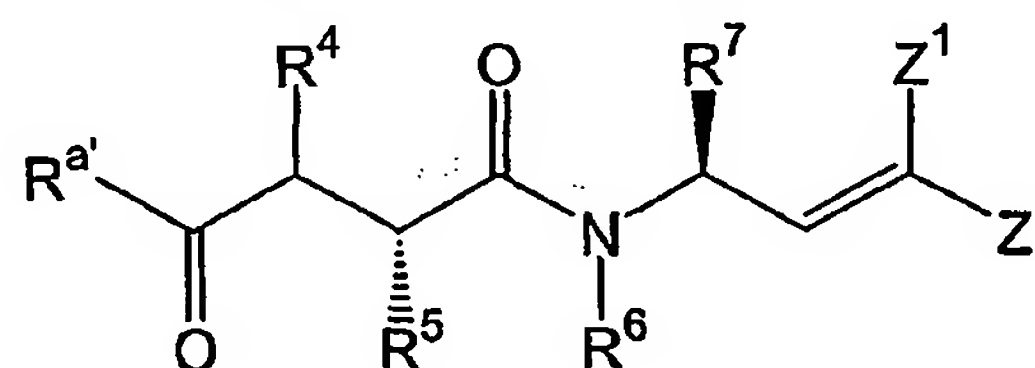
41. The compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according one of claims 8, 12, 13, 19 or 20, wherein Z is selected from ethoxycarbonyl, t-butoxycarbonyl, isopropoxycarbonyl, (2,2-dimethylpropyl)-oxycarbonyl, benzyloxycarbonyl, pyridylmethylenoxycarbonyl, cyclobutyloxycarbonyl, cyclopentyloxycarbonyl, cyclohexyloxycarbonyl and cycloheptyloxycarbonyl, where the ethoxy, t-butoxy, isopropoxy, (2,2-dimethylpropyl)-oxy, benzyl, pyridylmethylen, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl moieties thereof are unsubstituted or substituted with one or more suitable substituents, or Z^1 and Z taken together with the atom to which they are attached form



42. The compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate according claim 41, wherein Z is selected from ethoxycarbonyl, t-butoxycarbonyl, isopropoxycarbonyl, (2,2-dimethylpropyl)-oxycarbonyl, benzyloxycarbonyl, pyridylmethylenoxycarbonyl, cyclobutyloxycarbonyl, cyclopentyloxycarbonyl, cyclohexyloxycarbonyl and cycloheptyloxycarbonyl, or Z¹ and Z taken together with the atom to which they are attached form

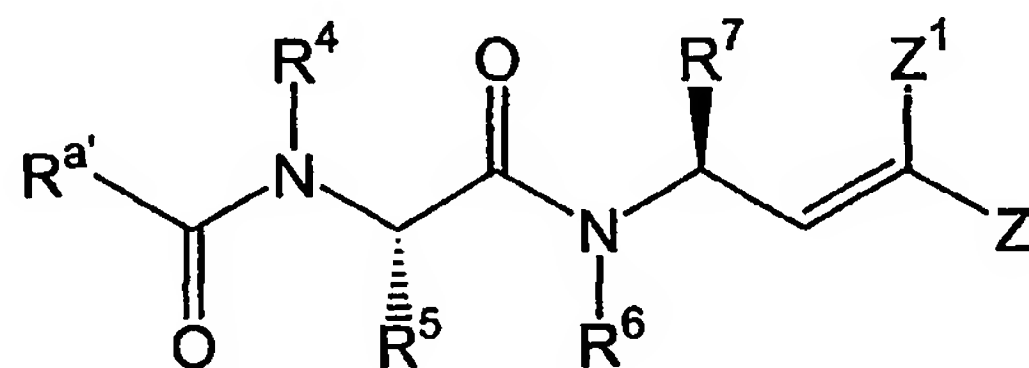


43. The compound according to claim 10, having the formula:



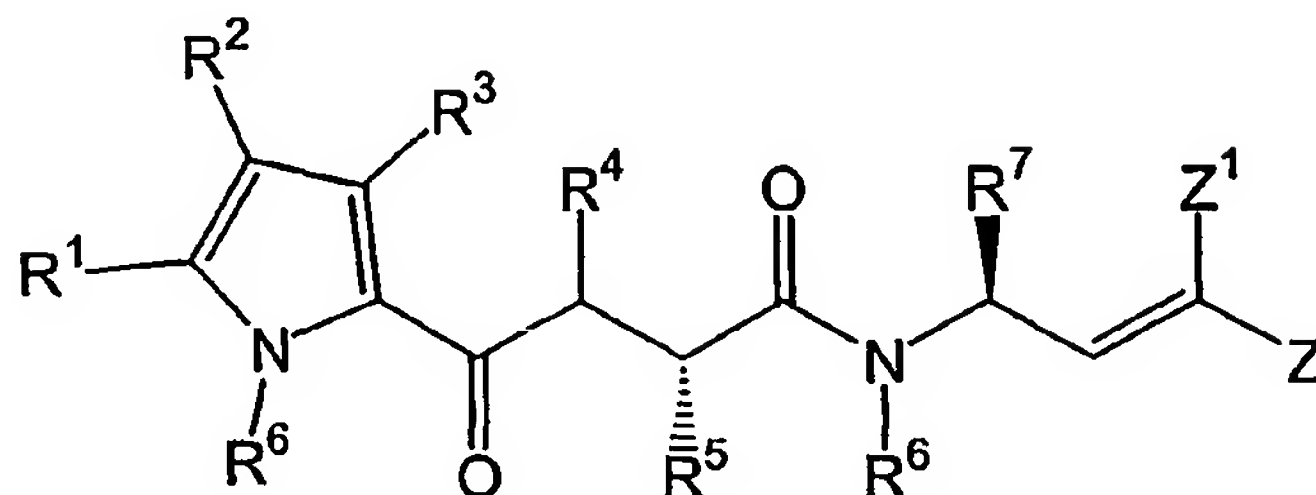
wherein R^{a'} is an alkyl, cycloalkyl, aryl or heteroaryl group, where said alkyl, cycloalkyl, aryl, and heteroaryl group is unsubstituted or substituted with one or more suitable substituents, and each R⁴, R⁵, R⁶, R⁷, Z and Z¹ are defined as in claim 10.

44. The compound according to claim 11, having the formula::



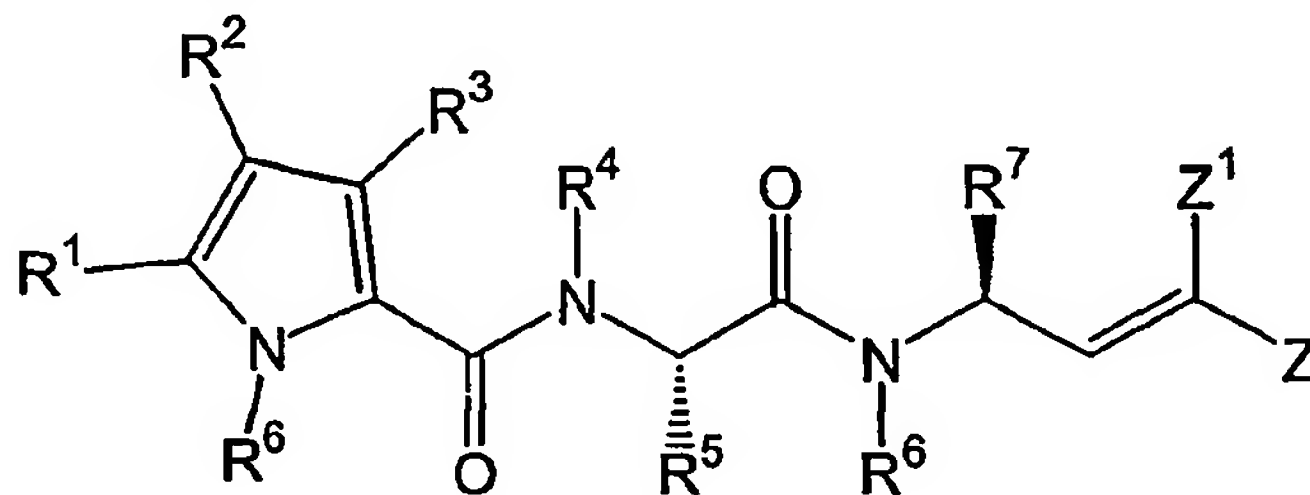
wherein R^{a'} is an alkyl, cycloalkyl, aryl or heteroaryl group, where said alkyl, cycloalkyl, aryl, and heteroaryl group is unsubstituted or substituted with one or more suitable substituents, and each R⁴, R⁵, R⁶, R⁷, Z and Z¹ are defined as in claim 11.

45. The compound according to claim 12, having the formula:



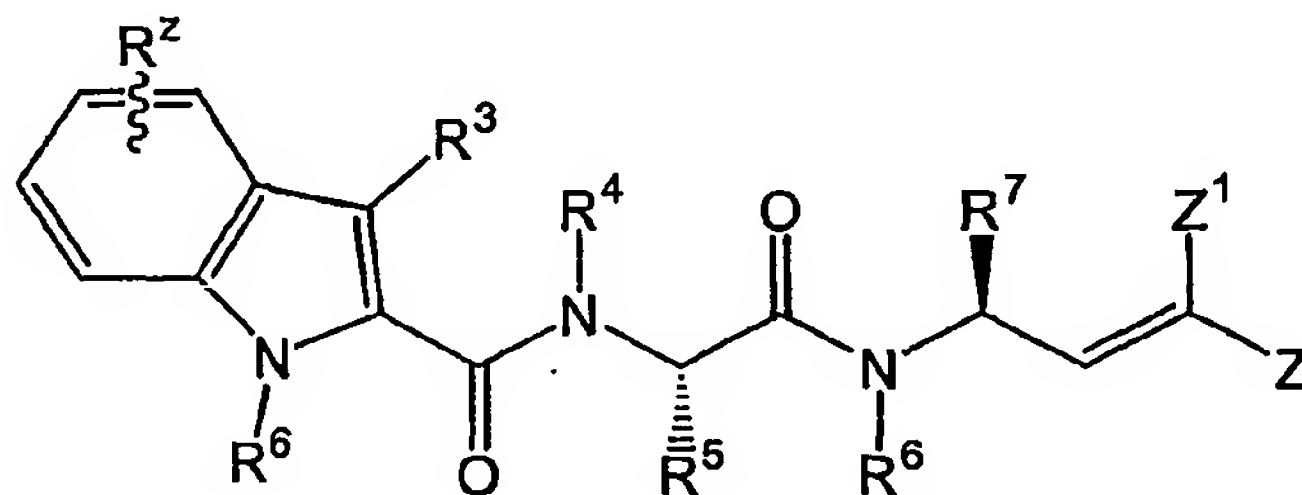
wherein R¹ is an alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group, where the alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl group is unsubstituted or substituted with one or more suitable substituents, and each R¹, R², R³, R⁴, R⁵, R⁶, R⁷, Z and Z¹ are defined as in claim 12.

46. The compound according to claim 13, having the formula:



wherein R¹, R², R³, R⁴, R⁵, R⁶, R⁷, Z and Z¹ are defined as in claim 13.

47. The compound according to claim 14, having the formula:

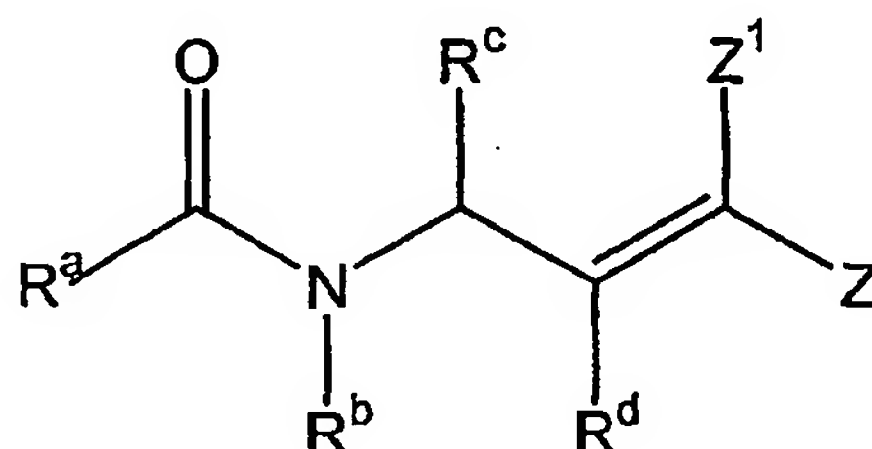


wherein R², R³, R⁴, R⁵, R⁶, R⁷, Z and Z¹ are defined as in claim 14.

48. The compound according to claims 12 or 13, wherein R¹ is selected from H and a lower alkyl, phenyl, naphthyl, pyridyl, quinoyl, isoquinoyl or isoxazoyl group, where the lower alkyl, phenyl, naphthyl, pyridyl, quinoyl, isoquinoyl or isoxazoyl group is

unsubstituted or substituted with one or more substituents selected from alkyl, hydroxy, halo, haloalkyl, alkoxy, haloalkoxy and alkylenedioxy moiety.

49. An antipicornaviral compound having the formula:

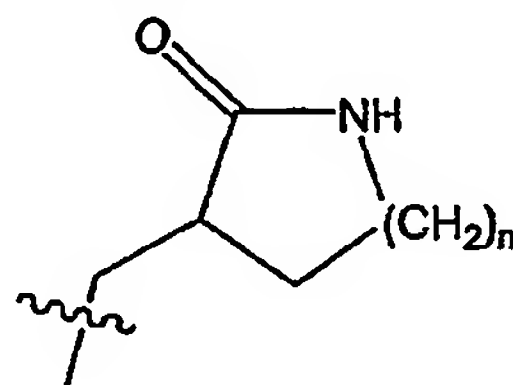


wherein:

R^a is (C_1-C_4) alkylcarbonyl- (C_1-C_4) alkyl, (C_3-C_8) cycloalkylcarbonyl- (C_1-C_4) alkyl, arylcarbonyl- (C_1-C_4) alkyl, heteroarylcarbonyl- (C_1-C_4) alkyl, (C_1-C_4) alkylcarbonylamino- (C_1-C_4) alkyl, (C_3-C_8) cycloalkylcarbonylamino- (C_1-C_4) alkyl, heterocycloalkylcarbonylamino- (C_1-C_4) alkyl, arylcarbonylamino- (C_1-C_4) alkyl, heteroarylcarbonylamino- (C_1-C_4) alkyl, (C_1-C_4) alkylaminocarbonyl- (C_1-C_4) alkyl, (C_3-C_8) cycloalkylaminocarbonyl- (C_1-C_4) alkyl, heterocycloalkylaminocarbonyl- (C_1-C_4) alkyl, arylaminocarbonyl- (C_1-C_4) alkyl, heteroarylaminocarbonyl- (C_1-C_4) alkyl, wherein each (C_1-C_4) alkyl, (C_3-C_8) cycloalkyl, heterocycloalkyl, aryl and heteroaryl moiety thereof is unsubstituted or substituted with one or more suitable substituents;

R^b and R^d are each independently H or C_1-C_4 alkyl;

R^c is selected from $-CH_2CH_2C(O)NH_2$; $-CH_2CH_2C(O)NH$ -alkyl;



$-CH_2NHC(O)CH_3$; and

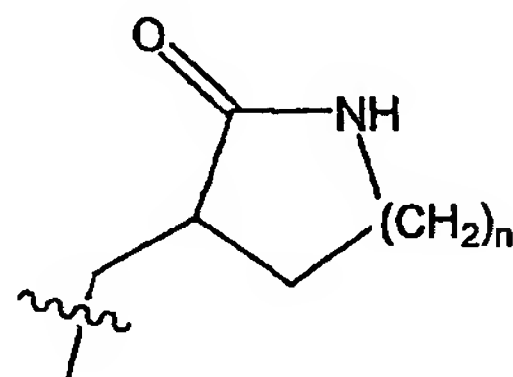
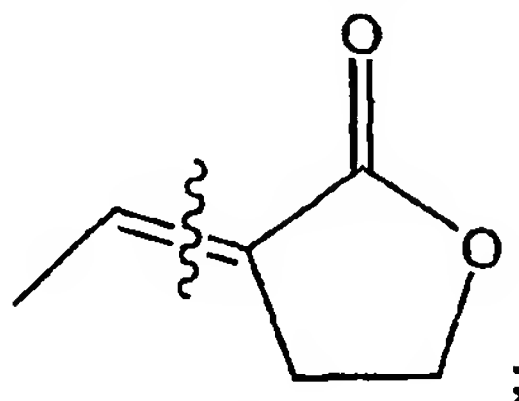
, where n is 1 or 2; and

Z^1 is H or C_1-C_4 alkyl and Z is $-CO_2$ -alkyl, $-CO_2$ -cycloalkyl,

- 172 -

-CO₂-alkylaryl or -CO₂-alkylheterocycloaryl, or Zⁱ and Z taken together with the atom

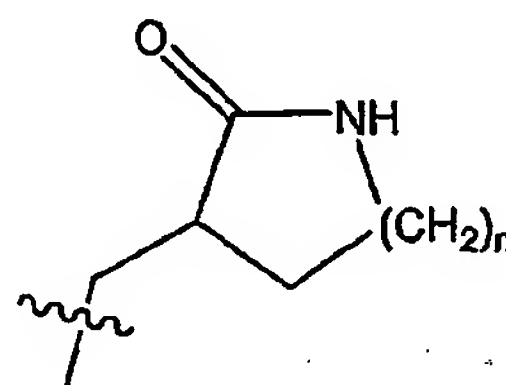
to which they are attached form



provided that R^c is

, where n is 1 or 2 when R^a

is an indolylcarbonylamino-(C₁-C₄)alkyl group where the indolyl moiety thereof is substituted with one or more suitable substituents or R^a is not an amino-substituted (C₁-C₄)alkylcarbonylamino-(C₁-C₄)alkyl or R^a is not an amino-substituted (C₁-C₄)alkylcarbonyl-(C₁-C₄)alkyl; and R^c is selected from -CH₂CH₂C(O)NH₂;



-CH₂CH₂C(O)NH-alkyl; -CH₂NHC(O)CH₃; and

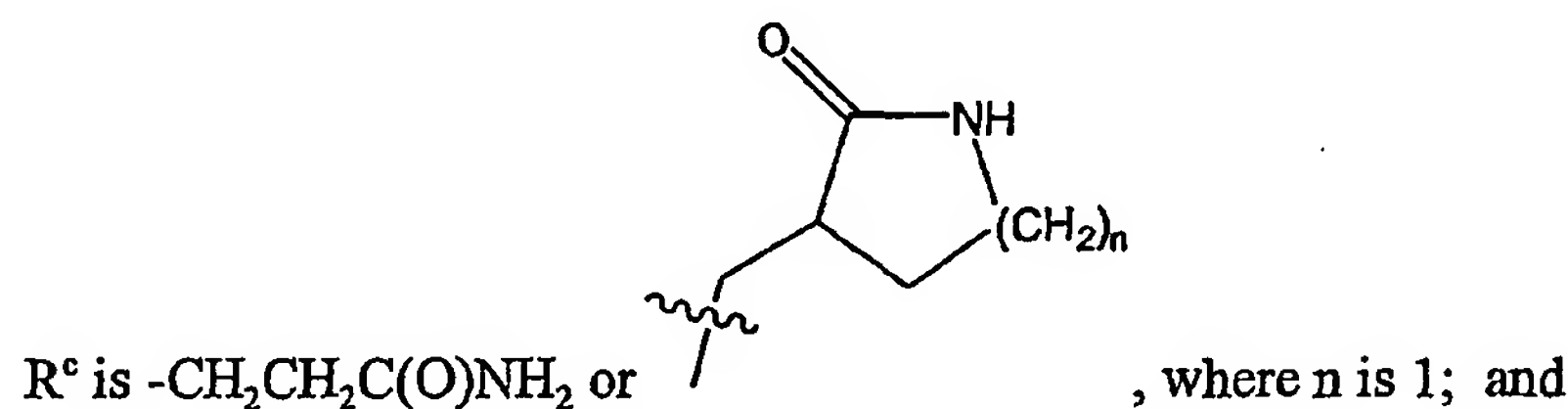
where n is 1 or 2, when R^a is an indolylcarbonylamino-(C₁-C₄)alkyl group where the indolyl moiety thereof is unsubstituted or R^a is a (C₁-C₄)alkylaminocarbonyl-(C₁-C₄)alkyl, (C₃-C₈)cycloalkylaminocarbonyl-(C₁-C₄)alkyl, heterocycloalkylaminocarbonyl-(C₁-C₄)alkyl, arylaminocarbonyl-(C₁-C₄)alkyl, heteroarylaminocarbonyl-(C₁-C₄)alkyl, or heteroarylcarbonylamino-(C₁-C₄)alkyl group, wherein each (C₁-C₄)alkyl, (C₃-C₈)cycloalkyl, heterocycloalkyl, aryl and heteroaryl moiety thereof is unsubstituted or substituted with one or more suitable substituents.

50. The compound according to claim 49, wherein:

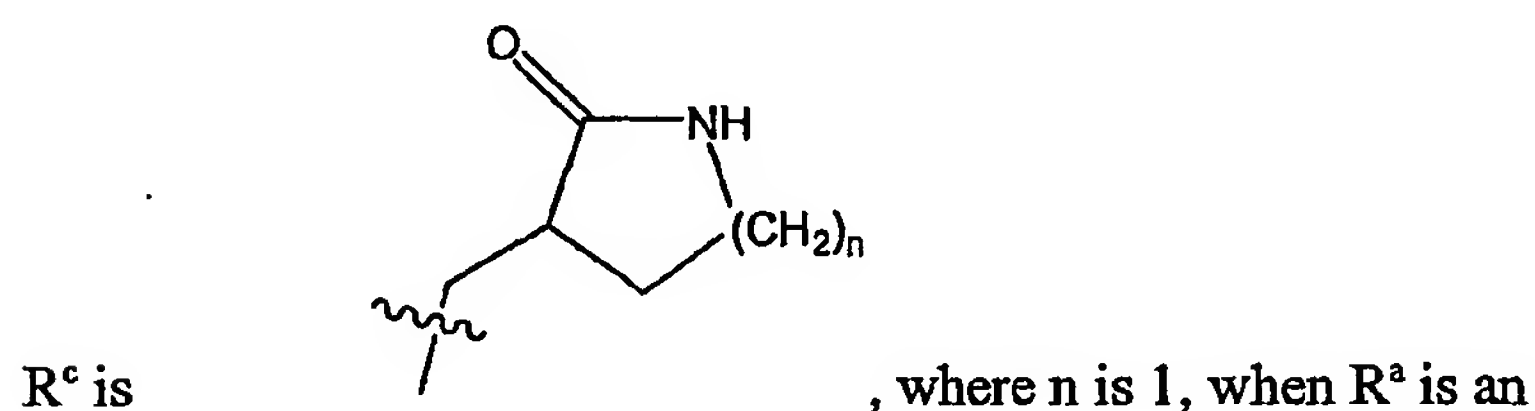
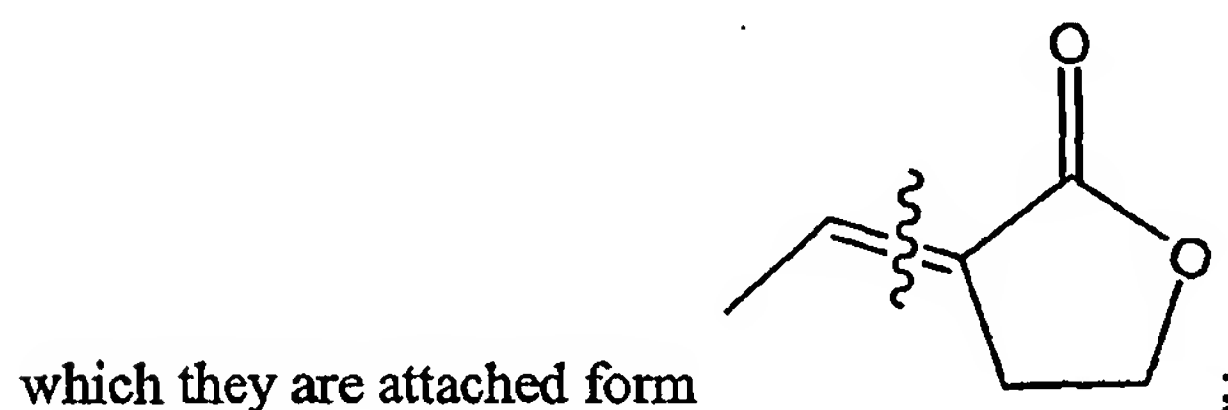
R^a is (C₁-C₄)alkylcarbonyl-(C₁-C₄)alkyl, (C₅-C₆)cycloalkylcarbonyl-(C₁-C₄)alkyl, arylcarbonyl-(C₁-C₄)alkyl, heteroarylcarbonyl-(C₁-C₄)alkyl, (C₁-C₄)alkylcarbonylamino-(C₁-C₄)alkyl, C₃-C₈ cycloalkylcarbonylamino-(C₁-C₄)alkyl, heterocycloalkylcarbonylamino-(C₁-C₄)alkyl, arylcarbonylamino-(C₁-C₄)alkyl, heteroarylcarbonylamino-(C₁-C₄)alkyl, (C₁-C₄)alkylaminocarbonyl-(C₁-C₄)alkyl,

- 173 -

(C₅-C₆)cycloalkylaminocarbonyl-(C₁-C₄)alkyl, heterocycloalkylaminocarbonyl-(C₁-C₄)alkyl, arylaminocarbonyl-(C₁-C₄)alkyl, heteroarylaminocarbonyl-(C₁-C₄)alkyl, wherein each (C₁-C₄)alkyl, (C₃-C₈)cycloalkyl, heterocycloalkyl, aryl and heteroaryl moiety thereof is unsubstituted or substituted with one or more suitable substituents;

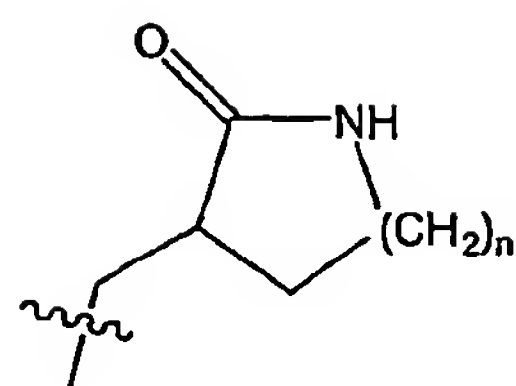


Z¹ is H and Z is -CO₂CH₂CH₃, -CO₂(CH(CH₃)₂), -CO₂(C(CH₃)₃), -CO₂CH₂(C(CH₃)₃), -CO₂(cyclo-C₅H₉) or Z¹ and Z taken together with the atom to



indolylcarbonylamino-(C₁-C₄)alkyl group where the indolyl moiety thereof is substituted with one or two substituents independently selected from halo, C₁-C₄ alkoxy, unsubstituted C₁-C₄ alkyl and C₁-C₄ haloalkyl, C₁-C₄ haloalkoxy, methylenedioxy, aryl, heterocycloalkyl, and heteroaryl where the aryl, heterocycloalkyl and heteroaryl is unsubstituted or substituted by one or more substituents independently selected from halo, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy and methylenedioxy; and R^c is selected from -CH₂CH₂C(O)NH₂; -CH₂CH₂C(O)NH-alkyl; -CH₂NHC(O)CH₃;

- 174 -



and , where n is 1, when R^a is

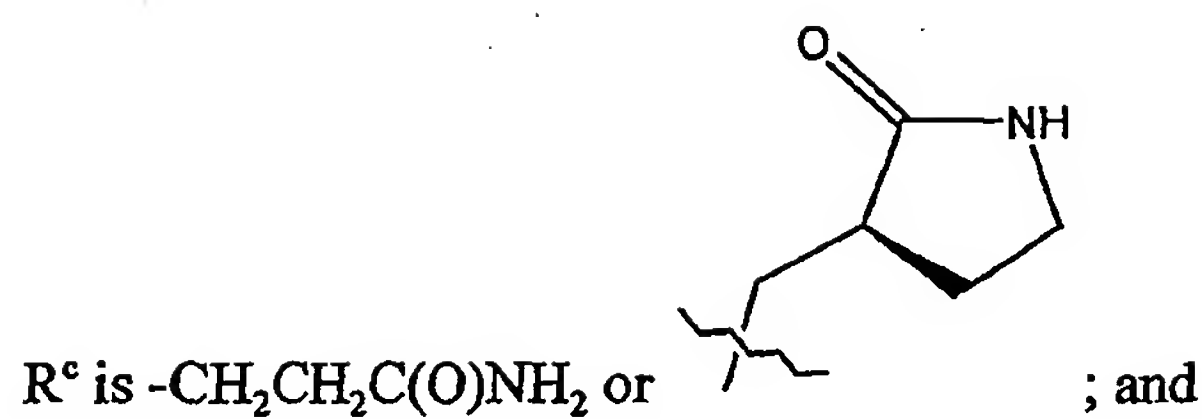
(C₁-C₄)alkylcarbonyl-(C₁-C₄)alkyl, (C₅-C₆)cycloalkyl carbonyl-(C₁-C₄)alkyl, arylcarbonyl-(C₁-C₄)alkyl, heteroarylcarbonyl-(C₁-C₄)alkyl, (C₁-C₄)alkylcarbonylamino-(C₁-C₄)alkyl, C₃-C₈ cycloalkylcarbonylamino-(C₁-C₄)alkyl, heterocycloalkylcarbonylamino-(C₁-C₄)alkyl, arylcarbonylamino-(C₁-C₄)alkyl, heteroarylcarbonylamino-(C₁-C₄)alkyl, (C₁-C₄)alkylaminocarbonyl-(C₁-C₄)alkyl, (C₃-C₈)cycloalkylaminocarbonyl-(C₁-C₄)alkyl, heterocycloalkylaminocarbonyl-(C₁-C₄)alkyl, arylaminocarbonyl-(C₁-C₄)alkyl, heteroarylaminocarbonyl-(C₁-C₄)alkyl, wherein each (C₁-C₄)alkyl, (C₃-C₈)cycloalkyl, heterocycloalkyl, aryl and heteroaryl moiety thereof unsubstituted or substituted with one or more suitable substituents.

51. The compound according to claim 49, wherein:

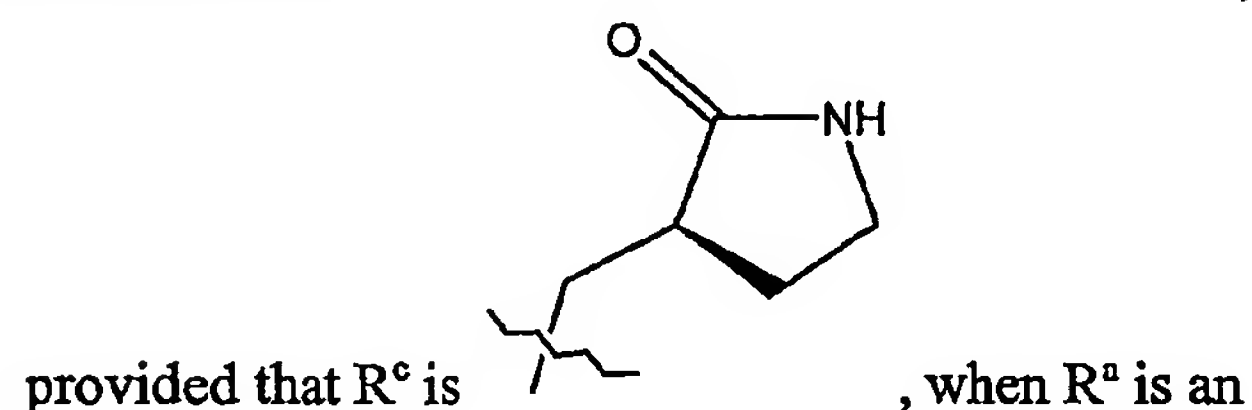
R^a is (C₁-C₄)alkylcarbonyl-(C₁-C₄)alkyl, phenylcarbonyl-(C₁-C₄)alkyl, naphthylcarbonyl-(C₁-C₄)alkyl, pyrrolylcarbonyl-(C₁-C₄)alkyl, indolylcarbonyl-(C₁-C₄)alkyl, (C₁-C₄)alkylcarbonylamino-(C₁-C₄)alkyl, pyrrolylcarbonylamino-(C₁-C₄)alkyl, indolylcarbonylamino-(C₁-C₄)alkyl, phenylcarbonylamino-(C₁-C₄)alkyl, naphthylcarbonylamino-(C₁-C₄)alkyl, (C₁-C₄)alkylaminocarbonyl-(C₁-C₄)alkyl, phenylaminocarbonyl-(C₁-C₄)alkyl, naphthylaminocarbonyl-(C₁-C₄)alkyl, wherein each (C₁-C₄)alkyl, phenyl, naphthyl, pyrrolyl, and indolyl moiety thereof is unsubstituted or substituted with one or more substituents independently selected from halo, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, methylenedioxy, aryl, heterocycloalkyl, and heteroaryl, where the aryl, heterocycloalkyl or heteroaryl is unsubstituted or substituted by one or more substituents independently selected from halo, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy and methylenedioxy;

R^b and R^d are each H;

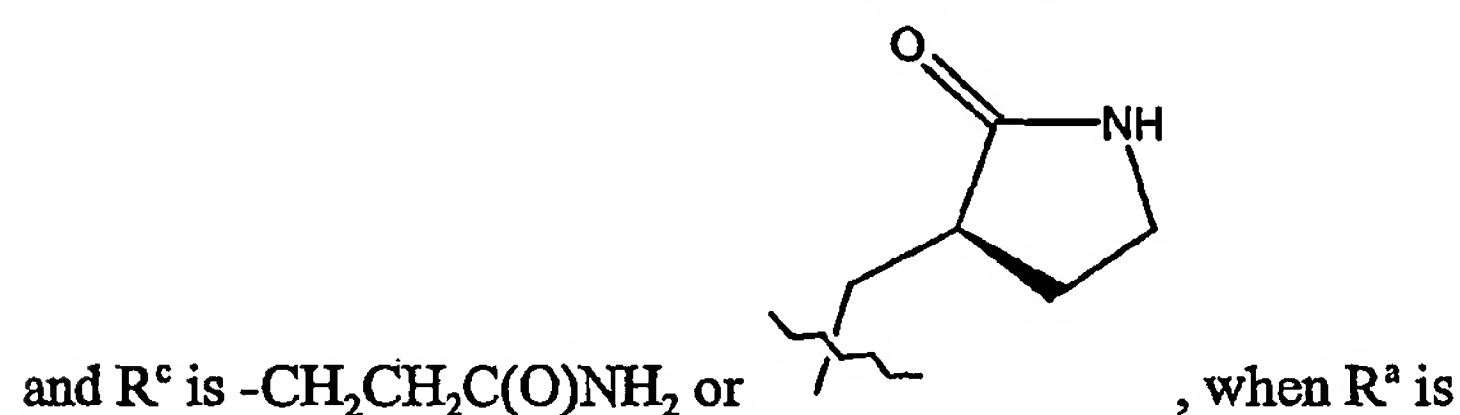
- 175 -



Z^1 is H and Z is $-\text{CO}_2\text{CH}_2\text{CH}_3$ or Z^1 and Z taken together with the atom to which



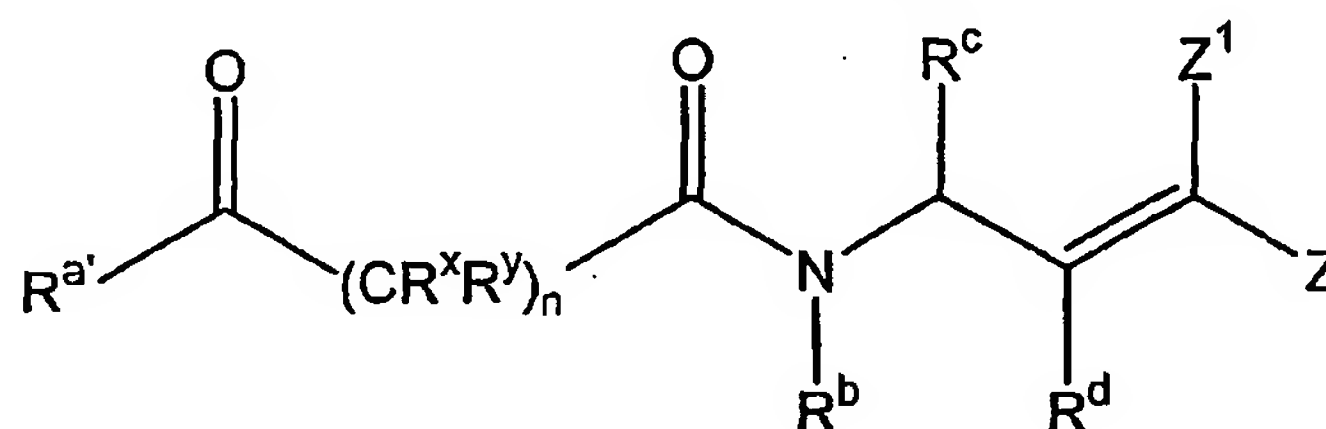
indolylcarbonylamino-($\text{C}_1\text{-C}_4$)alkyl group where the indolyl moiety thereof is substituted with one or two substituents independently selected from halo, $\text{C}_1\text{-C}_4$ alkoxy, unsubstituted $\text{C}_1\text{-C}_4$ alkyl and $\text{C}_1\text{-C}_4$ haloalkyl; and



($\text{C}_1\text{-C}_4$)alkylcarbonyl-($\text{C}_1\text{-C}_4$)alkyl, phenylcarbonyl-($\text{C}_1\text{-C}_4$)alkyl, naphthylcarbonyl-($\text{C}_1\text{-C}_4$)alkyl, pyrrolylcarbonyl-($\text{C}_1\text{-C}_4$)alkyl, indolylcarbonyl-($\text{C}_1\text{-C}_4$)alkyl, ($\text{C}_1\text{-C}_4$)alkylcarbonylamino-($\text{C}_1\text{-C}_4$)alkyl, pyrrolylcarbonylamino-($\text{C}_1\text{-C}_4$)alkyl, indolylcarbonylamino-($\text{C}_1\text{-C}_4$)alkyl, phenylcarbonylamino-($\text{C}_1\text{-C}_4$)alkyl, naphthylcarbonylamino-($\text{C}_1\text{-C}_4$)alkyl, ($\text{C}_1\text{-C}_4$)alkylaminocarbonyl-($\text{C}_1\text{-C}_4$)alkyl, phenylaminocarbonyl-($\text{C}_1\text{-C}_4$)alkyl, naphthylaminocarbonyl-($\text{C}_1\text{-C}_4$)alkyl, wherein each ($\text{C}_1\text{-C}_4$)alkyl, phenyl, naphthyl and pyrrolyl moiety thereof is group is unsubstituted or substituted with one or more substituents independently selected from halo, $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_1\text{-C}_4$ haloalkyl, $\text{C}_1\text{-C}_4$ alkoxy, $\text{C}_1\text{-C}_4$ haloalkoxy, methylenedioxy, aryl, heterocycloalkyl, and heteroaryl,

where the aryl, heterocycloalkyl and heteroaryl is unsubstituted or substituted by one or more substituents independently selected from halo, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy and methylenedioxy; and said indolyl moiety is unsubstituted.

52. The compound according to claim 49 having the formula:



wherein:

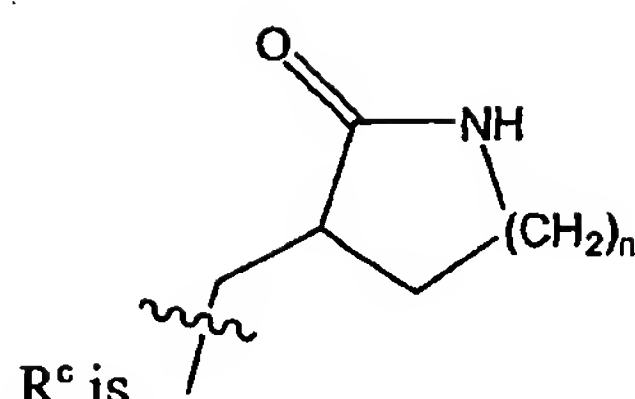
R^{a'} is a (C₁-C₄)alkyl, (C₃-C₈)cycloalkyl, aryl or heteroaryl group, wherein the (C₁-C₄)alkyl, (C₃-C₈)cycloalkyl, aryl and heteroaryl group is unsubstituted or substituted with one or more substituents independently selected from (C₁-C₄)alkyl, aryl, (C₃-C₈)cycloalkyl, heterocycloalkyl, heteroaryl, halo, hydroxyl, (C₁-C₄)alkoxy, alkylenedioxy, aryloxy, (C₃-C₈)cycloalkoxy, heteroaryloxy, and carboxyl where the (C₁-C₄)alkyl, aryl, (C₃-C₈)cycloalkyl, heterocycloalkyl, heteroaryl moieties thereof are optionally substituted by one or more of (C₁-C₄)alkyl, (C₁-C₄)haloalkyl or aryl, where the aryl is unsubstituted or substituted with one or more substituents independently selected from alkyl, haloalkyl, alkylenedioxy, nitro, amino, hydroxamino, alkylamino, dialkylamino, halo, hydroxyl, alkoxy, haloalkoxy, aryloxy, mercapto, alkylthio or arylthio;

R^b and R^d are each independently H or C₁-C₄ alkyl;

n is 1, 2 or 3;

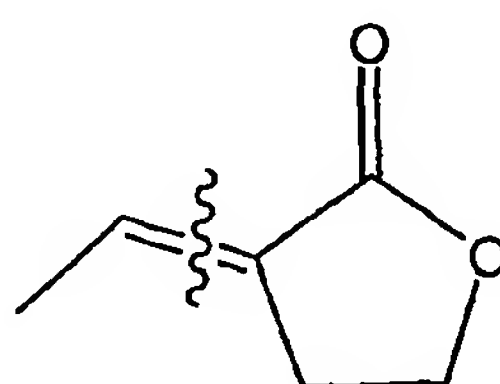
R^x is H and R^y is H, C₁-C₄ alkyl, C₁-C₄ haloalkyl or an arylalkyl, heteroarylalkyl, cycloalkylalkyl group or a straight-chain saturated hydrocarbon moiety or an unsaturated hydrocarbon moiety, where the arylalkyl, heteroarylalkyl, cycloalkylalkyl group is unsubstituted or substituted with one or more suitable substituents;

- 177 -



, where n is 1 or 2; and

Z^1 is H or C_1 - C_4 alkyl and Z is $-CO_2$ -alkyl, $-CO_2$ -cycloalkyl, $-CO_2$ -alkylaryl or $-CO_2$ -alkylheterocycloaryl, or Z^1 and Z taken together with the atom to which



they are attached form

53. The compound according to claim 52, wherein:

R^a is a $(C_1$ - $C_4)$ alkyl, pyrrolyl, indolyl, phenyl or naphthyl group, where the $(C_1$ - $C_4)$ alkyl group is unsubstituted or substituted with one or more substituents independently selected from halo, C_1 - C_4 alkoxy or C_1 - C_4 haloalkoxy and the pyrrolyl, indolyl, phenyl or naphthyl group is unsubstituted or substituted with one or more substituents independently selected from halo, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy, methylenedioxy, aryl, heterocycloalkyl and heteroaryl, where the aryl, heterocycloalkyl and heteroaryl is unsubstituted or substituted by one or more substituents independently selected from halo, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy and methylenedioxy

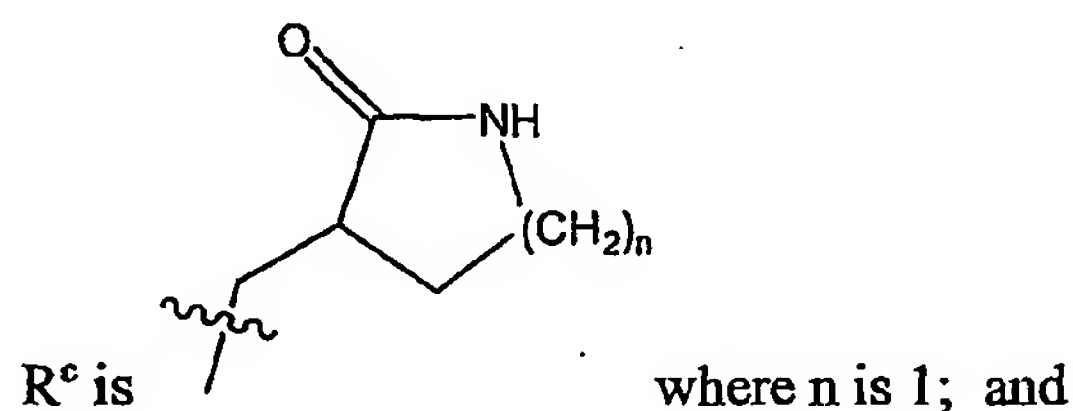
R^b and R^d are each H;

n is 1 or 2;

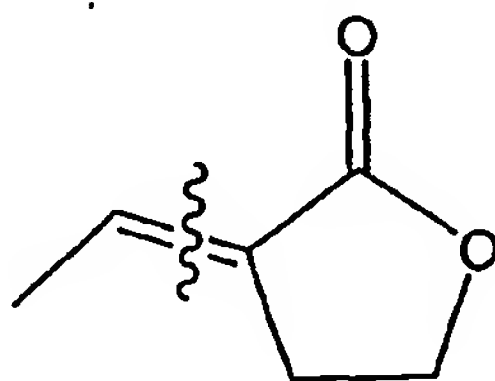
R^x is H and R^y is substituted or unsubstituted methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, -methylcyclohexyl, -methylthienyl or benzyl, where the substituted methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, and -methylcyclohexyl is substituted by one or more substituents independently selected from halo, alkoxy, aryloxy, alkylthio and arylthio; the substituted thienyl is substituted

- 178 -

by one or more substituents independently selected from lower alkyl, lower alkoxy, hydroxy, amino, alkylamino, dialkylamino and halo; and the phenyl moiety of the substituted benzyl is substituted by one or more substituents independently selected from lower alkyl, lower alkoxy, alkylenedioxy, hydroxy, amino, alkylamino, dialkylamino and halo;



Z^1 is H and Z is $-\text{CO}_2\text{CH}_2\text{CH}_3$, $-\text{CO}_2(\text{CH}(\text{CH}_3)_2)$, $-\text{CO}_2(\text{C}(\text{CH}_3)_3)$, $-\text{CO}_2\text{CH}_2(\text{C}(\text{CH}_3)_3)$, $-\text{CO}_2(\text{cyclo-C}_5\text{H}_9)$ or Z^1 and Z taken together with the atom to



which they are attached form

54. The compound according to claim 52, wherein:

R^a is an unsubstituted ($\text{C}_1\text{-C}_4$)alkyl, or a pyrrolyl, indolyl, phenyl or naphthyl group, where the pyrrolyl, indolyl, phenyl or naphthyl group is unsubstituted or substituted by one or more substituents independently selected from halo, $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_1\text{-C}_4$ haloalkyl or a phenyl, naphthyl, isoxazolyl, pyridyl, quinoyl or isoquinoyl group, where the phenyl, naphthyl, isoxazolyl, pyridyl, quinoyl or isoquinoyl group is unsubstituted or substituted with one or more substituents independently selected from halo, $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_1\text{-C}_4$ haloalkyl, $\text{C}_1\text{-C}_4$ alkoxy, $\text{C}_1\text{-C}_4$ haloalkoxy and methylenedioxy;

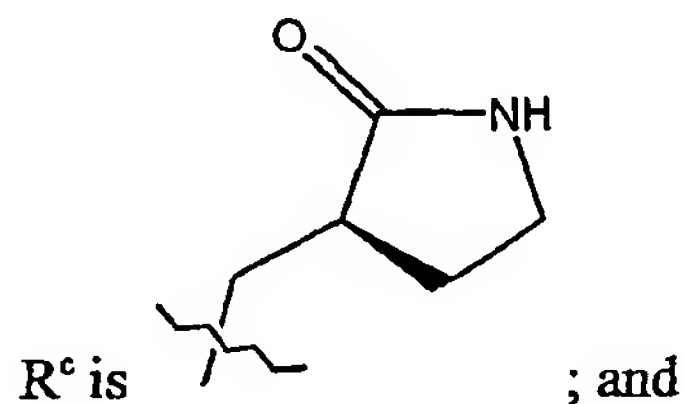
R^b and R^d are each H;

n is 2;

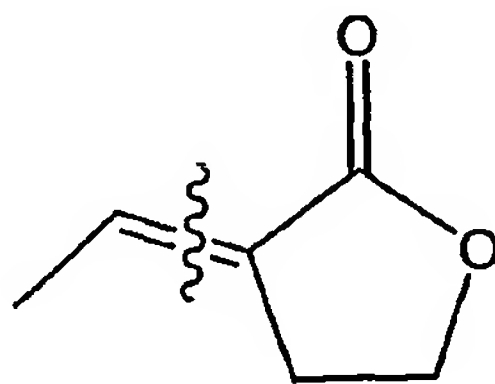
R^x is H and R^y is ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, -methylcyclohexyl, benzyl or substituted benzyl, wherein the phenyl moiety of the substituted benzyl

- 179 -

comprises one or more substituents independently selected from C₁-C₄ alkyl, C₁-C₄ alkoxy and halo;

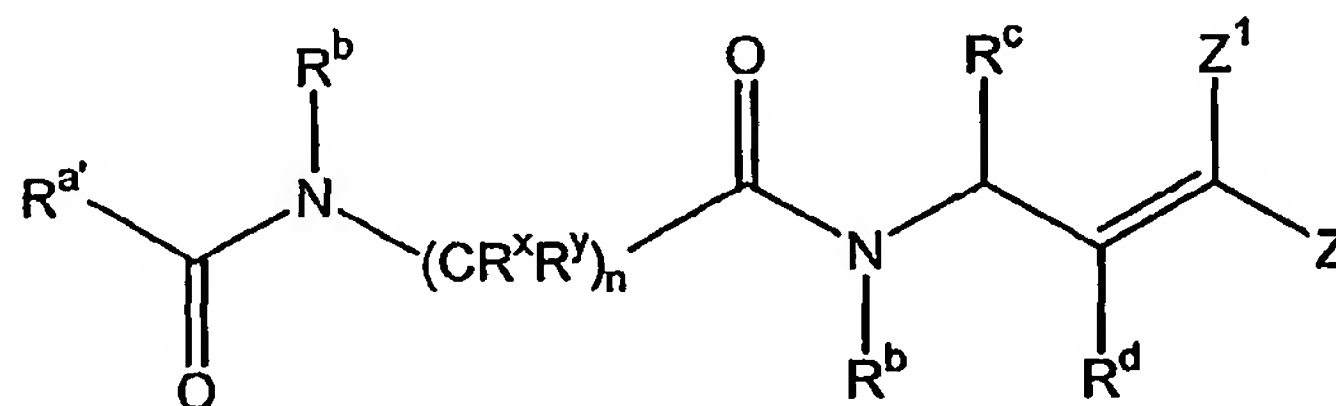


Z¹ is H and Z is -CO₂CH₂CH₃ or Z¹ and Z taken together with the atom to



which they are attached form

55. The compound according to claim 49, having the formula:



wherein:

R^a is a (C₁-C₄)alkyl, phenyl, naphthyl, pyrrolyl or indolyl group, where the (C₁-C₄)alkyl group is unsubstituted or substituted with one or more substituents independently selected from halo, C₁-C₄ alkoxy or C₁-C₄ haloalkoxy and the phenyl, naphthyl, pyrrolyl or indolyl group is unsubstituted or substituted with one or more substituents independently selected from halo, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, methylenedioxy, aryl, heterocycloalkyl, and heteroaryl, where the aryl, heterocycloalkyl or heteroaryl is unsubstituted or substituted by one or more substituents independently selected from halo, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy and methylenedioxy;

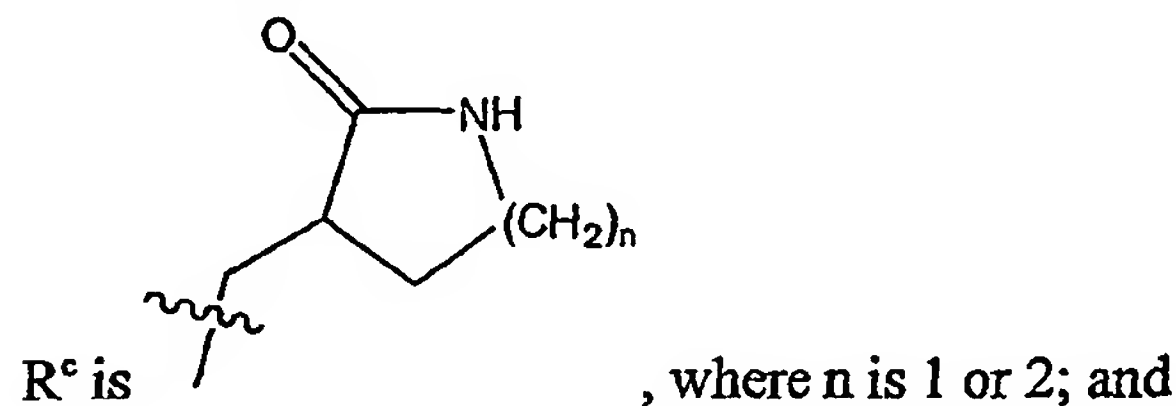
n is 1, 2 or 3,

R^x is H and R^y is H, C₁-C₄ alkyl, C₁-C₄ haloalkyl or an arylalkyl, heteroarylalkyl, cycloalkylalkyl group or a straight-chain saturated hydrocarbon moiety or an

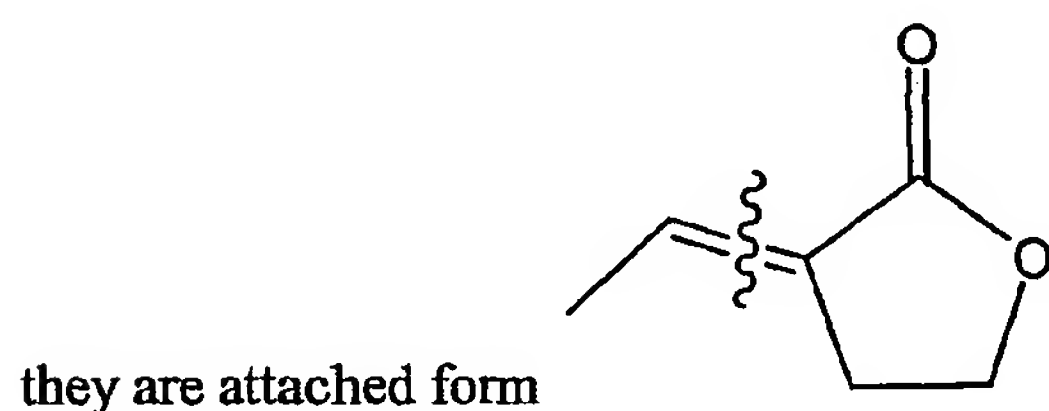
- 180 -

unsaturated hydrocarbon moiety, where the arylalkyl, heteroarylalkyl, cycloalkylalkyl group is unsubstituted or substituted with one or more suitable substituents.

R^b and R^d are each independently H or C_1 - C_4 alkyl;



Z^1 is H or C_1 - C_4 alkyl and Z is $-CO_2$ -alkyl, $-CO_2$ -cycloalkyl, $-CO_2$ -alkylaryl or $-CO_2$ -alkylheterocycloaryl, or Z^1 and Z taken together with the atom to which



56. The compound according to claim 55, wherein:

R^a is a pyrrolyl or indolyl group, where the pyrrolyl or indolyl group is unsubstituted or substituted by one or more substituents independently selected from halo, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl or a phenyl, naphthyl, isoxazolyl, pyridyl, quinoyl or isoquinoyl group, where the phenyl, naphthyl, isoxazolyl, pyridyl, quinoyl or isoquinoyl group is unsubstituted or substituted with one or more substituents independently selected from: halo, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy and methylenedioxy;

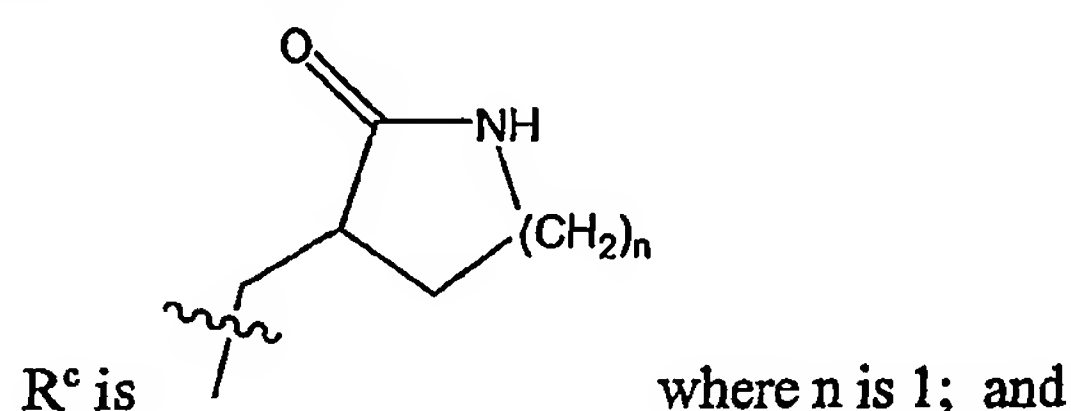
R^b and R^d are each H;

n is 1 or 2;

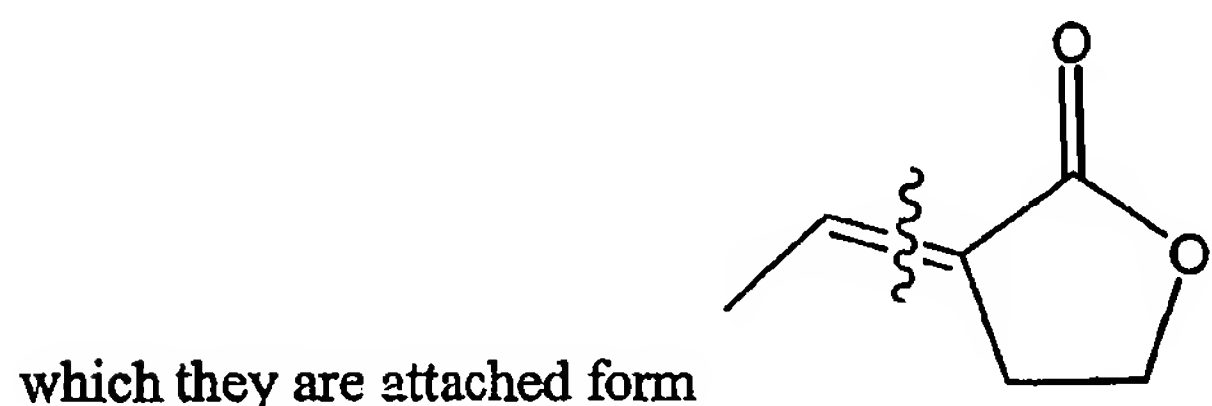
R^x is H and R^y is substituted or unsubstituted methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, -methylcyclohexyl, -methylthienyl or benzyl, where the substituted methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, and -methylcyclohexyl is substituted by one or more substituents independently selected

- 181 -

from halo, alkoxy, aryloxy, alkylthio and arylthio; the substituted thienyl is substituted by one or more substituents independently selected from lower alkyl, lower alkoxy, hydroxy, amino, alkylamino, dialkylamino and halo; and the phenyl moiety of the substituted benzyl is substituted by one or more substituents independently selected from lower alkyl, lower alkoxy, alkylenedioxy, hydroxy, amino, alkylamino, dialkylamino and halo;



Z^1 is H and Z is $-\text{CO}_2\text{CH}_2\text{CH}_3$, $-\text{CO}_2(\text{CH}(\text{CH}_3)_2)$, $-\text{CO}_2(\text{C}(\text{CH}_3)_3)$, $-\text{CO}_2\text{CH}_2(\text{C}(\text{CH}_3)_3)$, $-\text{CO}_2(\text{cyclo-C}_5\text{H}_9)$ or Z^1 and Z taken together with the atom to



57. The compound according to claim 55, wherein:

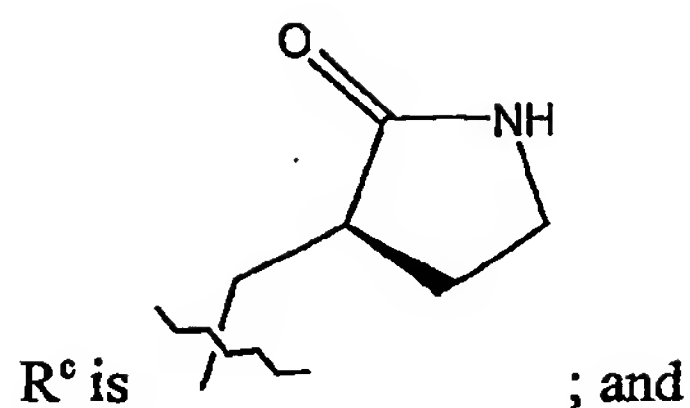
R^a is a pyrrolyl group that is unsubstituted or substituted by phenyl, α -naphthyl, β -naphthyl, 2-chlorophenyl, 2- α,α,α -trifluoromethylphenyl, 3-chloro-6-methoxyphenyl, 2,3-dichlorophenyl, 4-isoquinoyl, 3-iso-propylphenyl, 2,5-dimethoxyphenyl, 2-methoxyphenyl, 2-methylphenyl (o-tolyl), 2-bromophenyl, 3-pyridyl, 4-pyridyl, 3-methyl-isoxazol-5-yl, 3,3,3-trifluoroprop-1-yl, or 2,3-benzo[d]dioxolyl;

R^b and R^d are each H;

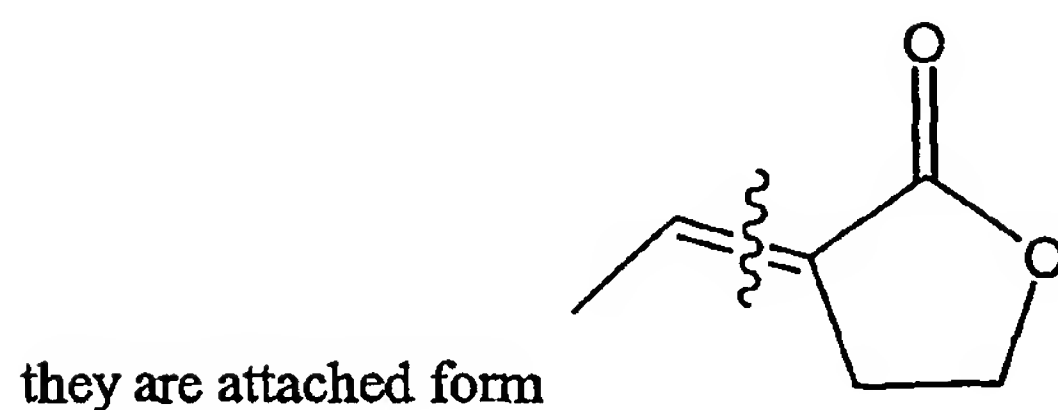
n is 1;

R^x is H and R^y is ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, -methylcyclohexyl, benzyl or substituted benzyl, wherein the phenyl moiety of the substituted benzyl comprises one or more substituents independently selected from C_1 - C_4 alkyl, C_1 - C_4 alkoxy and halo;

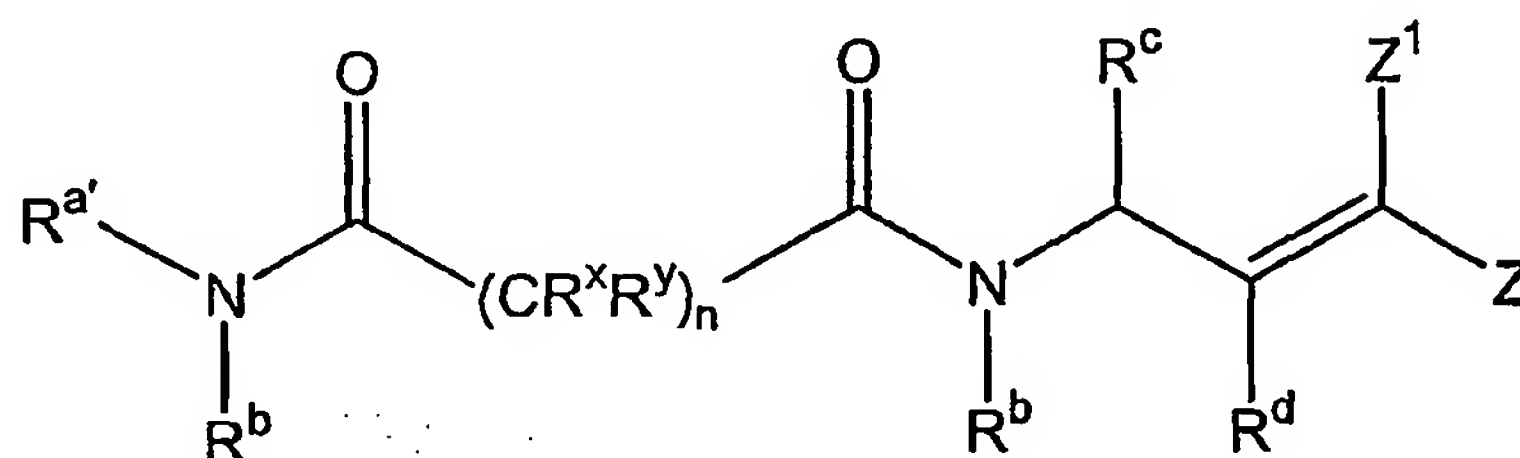
- 182 -



Z^1 is H and Z is $-\text{CO}_2\text{CH}_2\text{CH}_3$ or Z^1 and Z taken together with the atom to which



58. The compound according to claim 49, having the formula:



wherein:

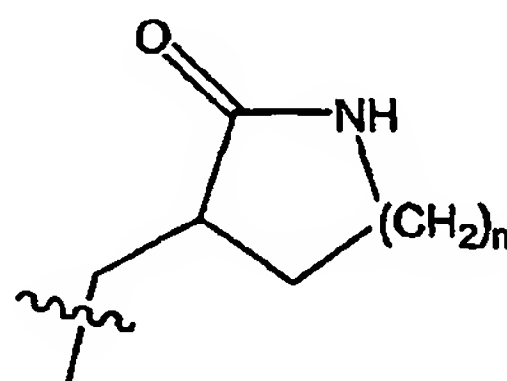
R^a is a $(\text{C}_1\text{-C}_4)$ alkyl, $(\text{C}_3\text{-C}_8)$ cycloalkyl, heterocycloalkyl, aryl or heteroaryl group, wherein the $(\text{C}_1\text{-C}_4)$ alkyl, $(\text{C}_3\text{-C}_8)$ cycloalkyl, heterocycloalkyl, aryl and heteroaryl group is unsubstituted or substituted with one or more suitable substituents;

n is 1, 2 or 3;

R^x is H and R^y is H, $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_1\text{-C}_4$ haloalkyl or an arylalkyl, heteroarylalkyl, cycloalkylalkyl group or a straight-chain saturated hydrocarbon moiety or an unsaturated hydrocarbon moiety, where the arylalkyl, heteroarylalkyl, cycloalkylalkyl group is unsubstituted or substituted with one or more suitable substituents;

R^c is selected from $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$; $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH-alkyl}$;

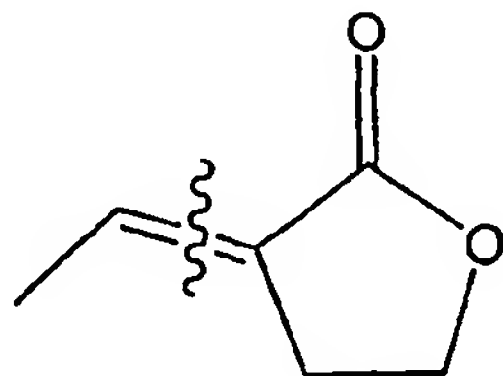
$-\text{CH}_2\text{NHC}(\text{O})\text{CH}_3$; and



, where n is 1 or 2; and

- 183 -

Z^1 is H or C_1 - C_4 alkyl and Z is $-\text{CO}_2$ -alkyl, $-\text{CO}_2$ -cycloalkyl, $-\text{CO}_2$ -alkylaryl or $-\text{CO}_2$ -alkylheterocycloaryl, or Z^1 and Z taken together with the atom to which they are



attached form

59. The compound according to claim 58, wherein:

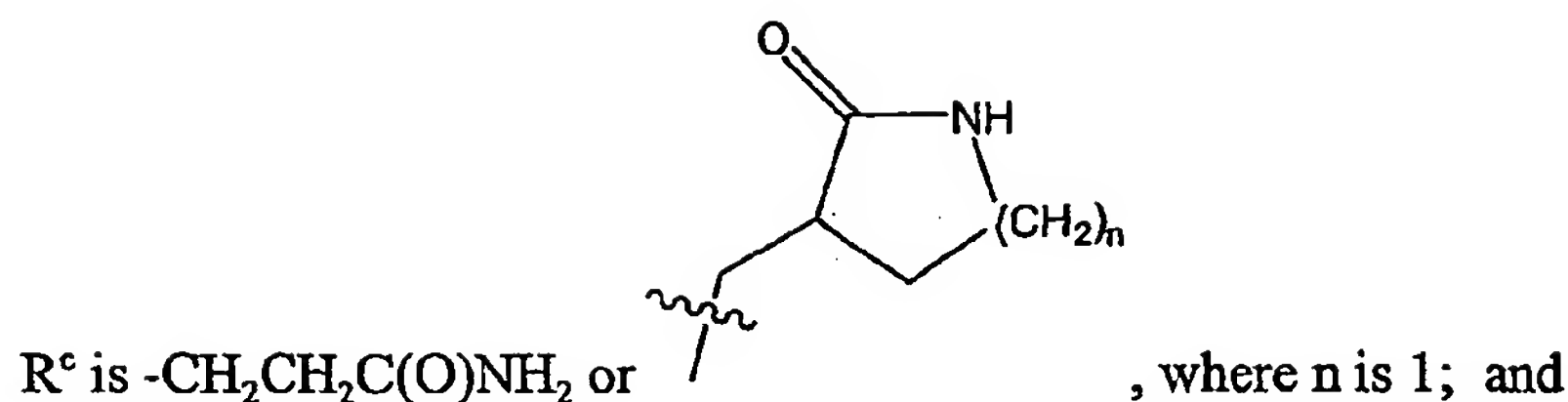
R^a is a $(C_1$ - $C_4)$ alkyl, phenyl or naphthyl group, where the $(C_1$ - $C_4)$ alkyl group is unsubstituted or substituted with one or more substituents independently selected from halo, C_1 - C_4 alkoxy or C_1 - C_4 haloalkoxy and the phenyl or naphthyl group is unsubstituted or substituted with one or more substituents independently selected from halo, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy, methylenedioxy and phenyl, where the phenyl is unsubstituted or substituted by one or more substituents independently selected from halo, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy and methylenedioxy;

n is 1 or 2;

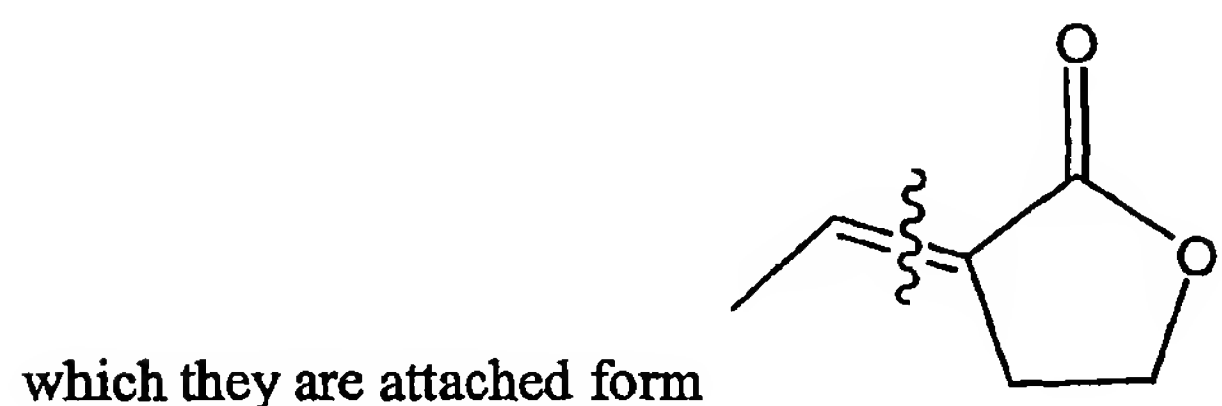
R^b and R^d are each H;

R^x is H and R^y is H or substituted or unsubstituted methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, -methylcyclohexyl, -methylthienyl or benzyl, where the substituted methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, and -methylcyclohexyl is substituted by one or more substituents independently selected from halo, alkoxy, aryloxy, alkylthio and arylthio; the substituted thienyl is substituted by one or more substituents independently selected from lower alkyl, lower alkoxy, hydroxy, amino, alkylamino, dialkylamino and halo; and the phenyl moiety of the substituted benzyl is substituted by one or more substituents independently selected from lower alkyl, lower alkoxy, alkylenedioxy, hydroxy, amino, alkylamino, dialkylamino and halo;

- 184 -



Z^1 is H and Z is $-\text{CO}_2\text{CH}_2\text{CH}_3$, $-\text{CO}_2(\text{CH}(\text{CH}_3)_2)$, $-\text{CO}_2(\text{C}(\text{CH}_3)_3)$, $-\text{CO}_2\text{CH}_2(\text{C}(\text{CH}_3)_3)$, $-\text{CO}_2(\text{cyclo-C}_5\text{H}_9)$ or Z^1 and Z taken together with the atom to



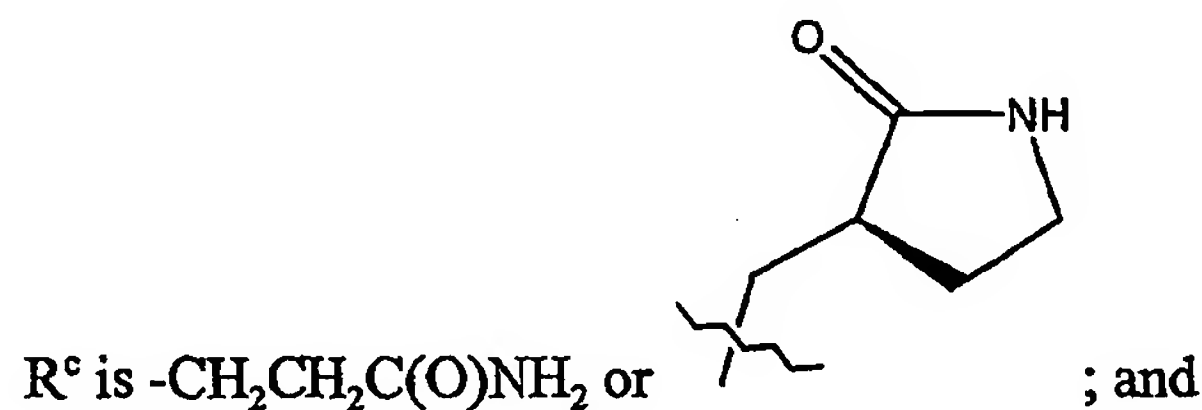
60. The compound according to claim 58, wherein:

R^a is a halo-substituted phenyl group;

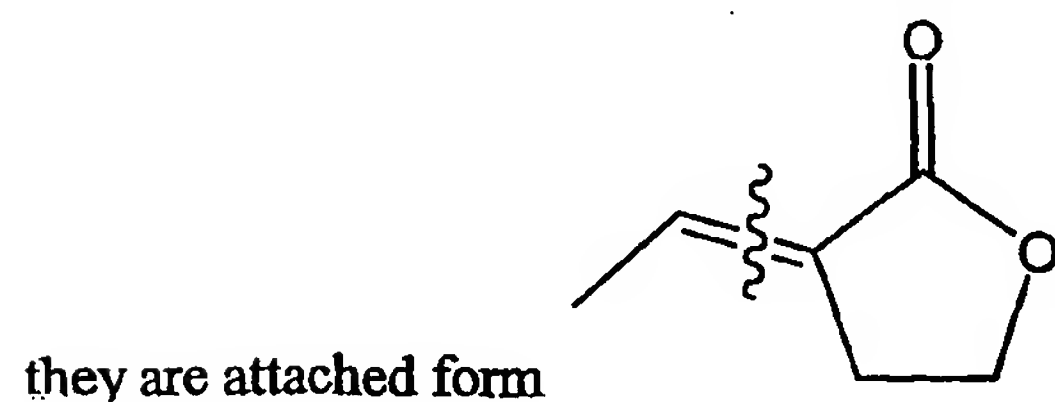
n is 2;

R^b and R^d are each H;

R^x is H and R^y is H, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, -methylcyclohexyl, benzyl or substituted benzyl, wherein the phenyl moiety of the substituted benzyl comprises one or more substituents independently selected from C_1 - C_4 alkyl, C_1 - C_4 alkoxy and halo;

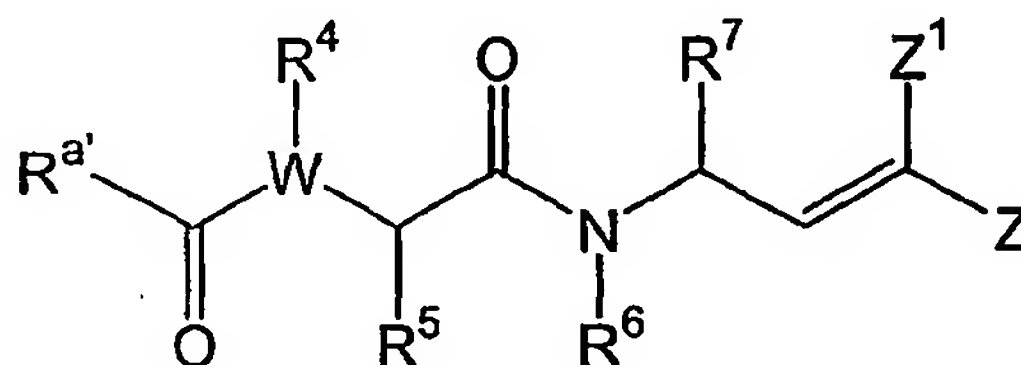


Z^1 is H and Z is $-\text{CO}_2\text{CH}_2\text{CH}_3$ or Z^1 and Z taken together with the atom to which



61. The compound according to any one of claims 52-60, wherein R^y is H, ethyl, 2-propyn-1-yl, methylcyclohexyl or benzyl.

62. An antipicornaviral compound having the formula:



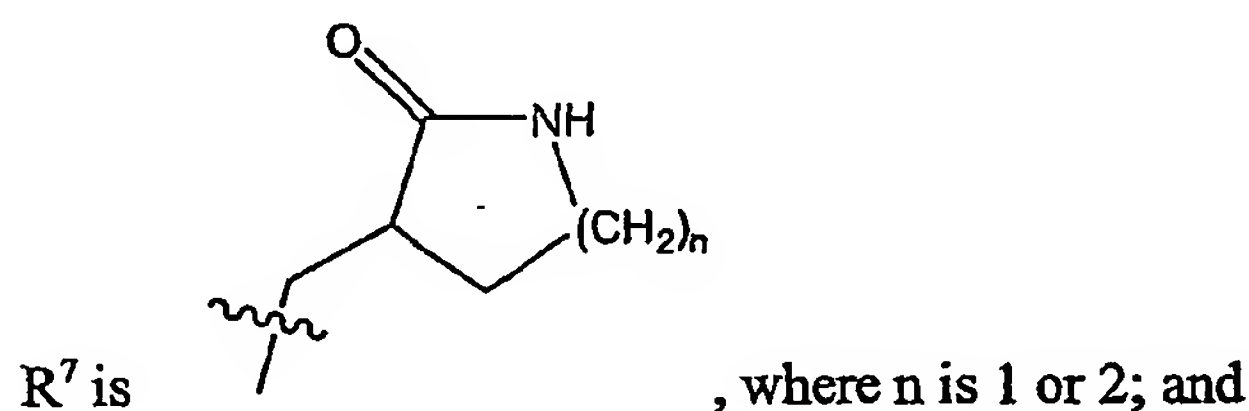
wherein:

W is CH or N;

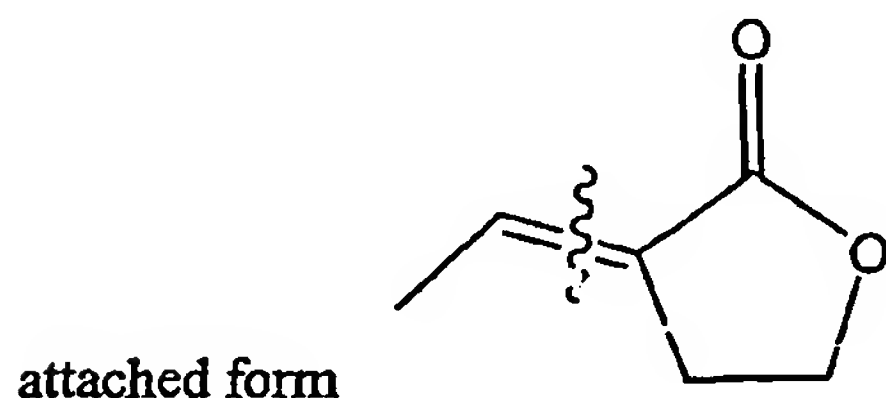
R^a is a C_1 - C_4 alkyl, C_3 - C_8 cycloalkyl, aryl or heteroaryl group, where the C_1 - C_4 alkyl, C_3 - C_8 cycloalkyl, aryl, and heteroaryl group is unsubstituted or substituted with one or more suitable substituents, provided that R^a is not an amino-substituted alkyl group;

R^4 and R^6 are each independently H or C_1 - C_4 alkyl;

R^5 is H, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl or an arylalkyl, heteroarylalkyl, cycloalkylalkyl group or a straight-chain saturated hydrocarbon moiety or an unsaturated hydrocarbon moiety, where the arylalkyl, heteroarylalkyl, cycloalkylalkyl group is unsubstituted or substituted with one or more suitable substituents;



Z^1 is H or C_1 - C_4 alkyl and Z is $-\text{CO}_2$ -alkyl, $-\text{CO}_2$ -cycloalkyl, $-\text{CO}_2$ -alkylaryl or $-\text{CO}_2$ -alkylheterocycloaryl, or Z^1 and Z taken together with the atom to which they are

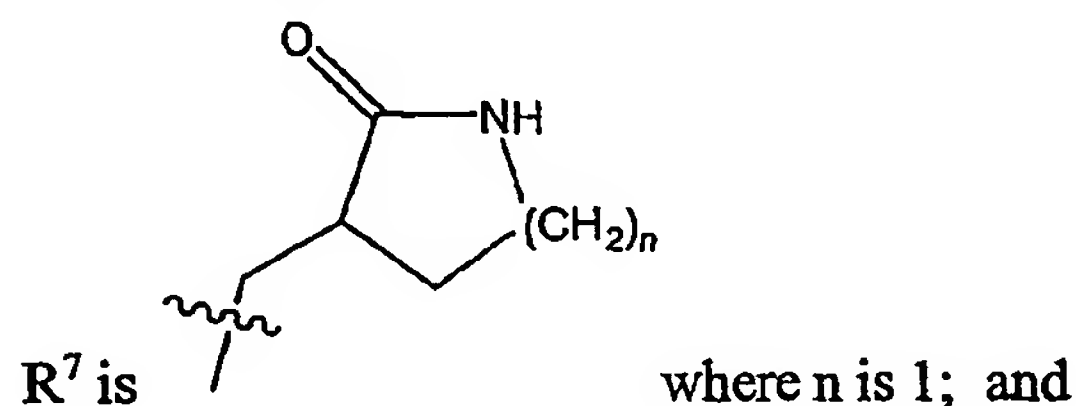


63. The compound according to claim 62, wherein:

R^a is a C_1 - C_4 alkyl, C_5 - C_6 cycloalkyl, phenyl, naphthyl or heteroaryl group, where the phenyl, naphthyl or heteroaryl group is unsubstituted or substituted with one or more substituents independently selected from halo, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy, methylenedioxy, aryl, heterocycloalkyl, and heteroaryl, where the aryl, heterocycloalkyl and heteroaryl is unsubstituted or substituted by one or more substituents independently selected from halo, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy and methylenedioxy;

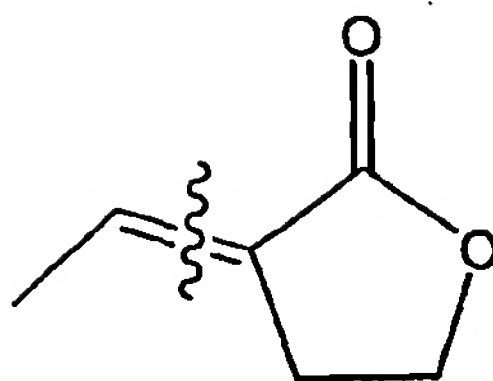
R^4 and R^6 are each H;

R^5 is H or substituted or unsubstituted methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, -methylcyclohexyl, -methylthienyl or benzyl, where the substituted methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, and -methylcyclohexyl is substituted by one or more substituents independently selected from halo, alkoxy, aryloxy, alkylthio and arylthio; the substituted thienyl is substituted by one or more substituents independently selected from lower alkyl, lower alkoxy, hydroxy, amino, alkylamino, dialkylamino and halo; and the phenyl moiety of the substituted benzyl is substituted by one or more substituents independently selected from lower alkyl, lower alkoxy, alkylenedioxy, hydroxy, amino, alkylamino, dialkylamino and halo;



Z^1 is H and Z is $-\text{CO}_2\text{CH}_2\text{CH}_3$, $-\text{CO}_2(\text{CH}(\text{CH}_3)_2)$, $-\text{CO}_2(\text{C}(\text{CH}_3)_3)$, $-\text{CO}_2\text{CH}_2(\text{C}(\text{CH}_3)_3)$, $-\text{CO}_2(\text{cyclo-C}_5\text{H}_9)$ or Z^1 and Z taken together with the atom to

- 187 -



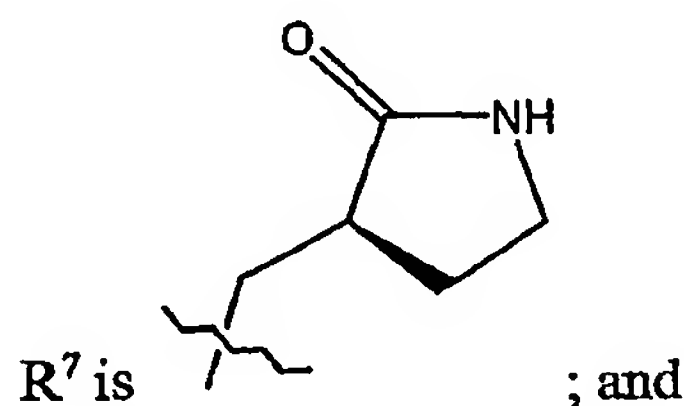
which they are attached form

64. The compound according to claim 62, wherein:

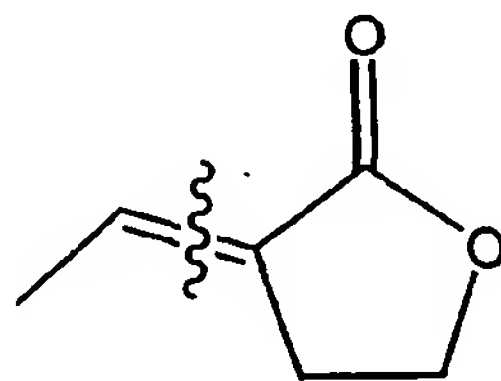
R^a is a C_1 - C_4 alkyl, C_5 - C_6 cycloalkyl, phenyl, naphthyl, pyrrolyl or indolyl, group, where the phenyl, naphthyl, pyrrolyl or indolyl, group is unsubstituted or substituted with one or more substituents independently selected from halo, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy, methylenedioxy and a phenyl, naphthyl, isoquinoyl, pyridyl or isoxazolyl group, wherein the phenyl, naphthyl, isoquinoyl, pyridyl and isoxazolyl group is unsubstituted or substituted by one or more substituents independently selected from halo, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy and methylenedioxy;

R^4 and R^6 are each H;

R^5 is H, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, -methylcyclohexyl, benzyl or substituted benzyl, wherein the phenyl moiety of the substituted benzyl comprises one or more substituents independently selected from C_1 - C_4 alkyl, C_1 - C_4 alkoxy and halo;

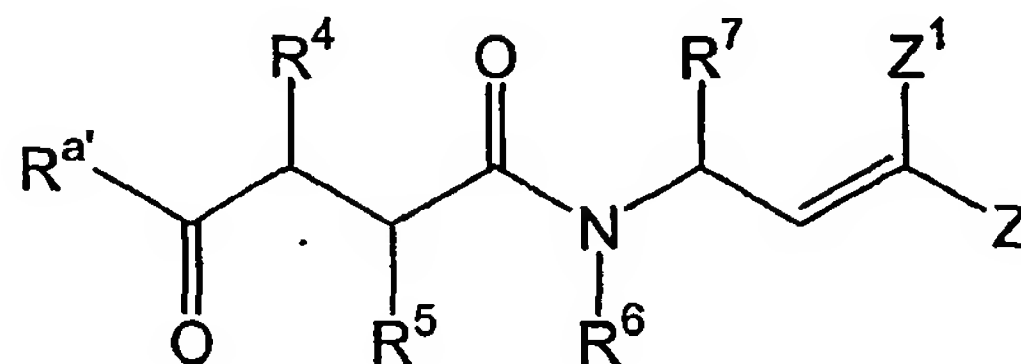


Z^1 is H and Z is $-\text{CO}_2\text{CH}_2\text{CH}_3$, or Z^1 and Z taken together with the atom to which

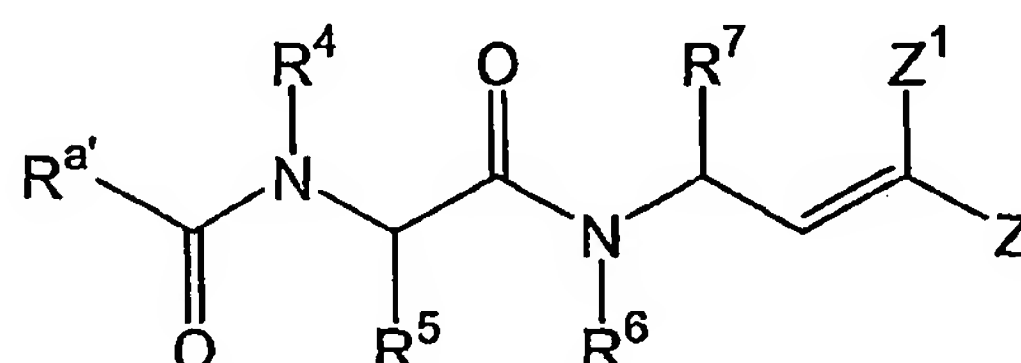


they are attached form

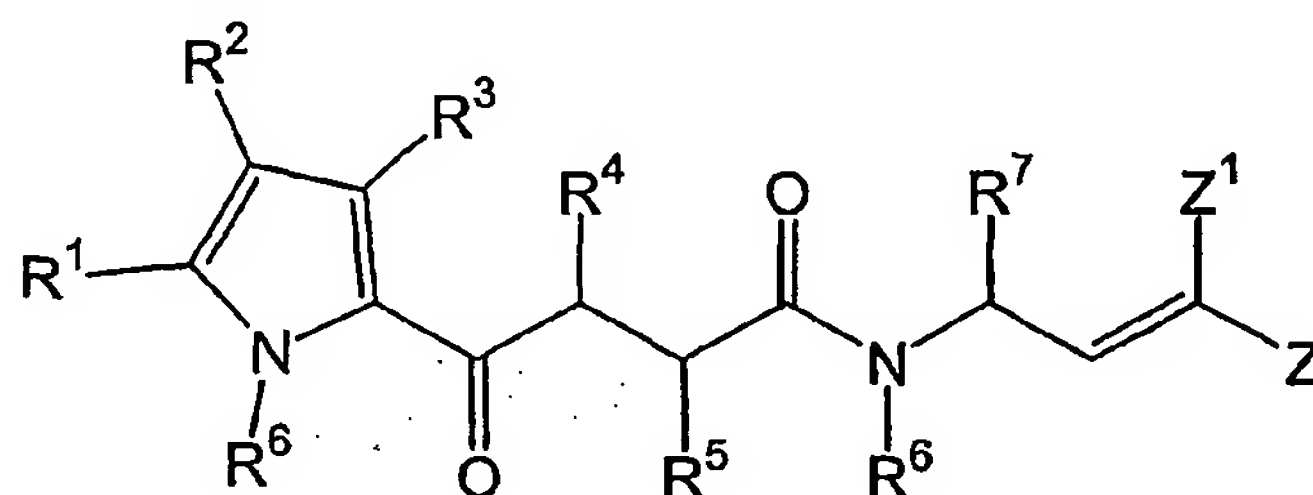
65. The compound according to claim 62, having the formula:



66. The compound according to claim 62, having the formula:



67. An antipicornaviral compound having the formula:



wherein:

R^1 is H, halo, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, or an aryl or heteroaryl group, where the aryl or heteroaryl group is unsubstituted or substituted with one or more suitable substituents;

R^2 and R^3 are each independently H or C_1 - C_4 alkyl; or

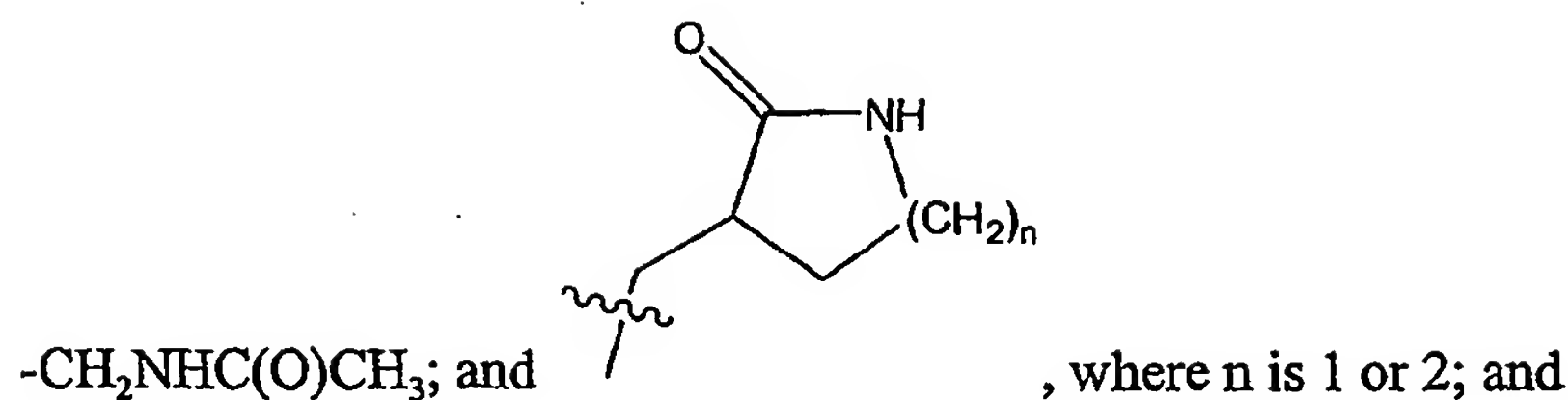
or R^1 together with R^2 form a cycloalkyl, heterocycloalkyl, aryl or heteroaryl ring, where the cycloalkyl, heterocycloalkyl, aryl or heteroaryl ring is unsubstituted or substituted with one or more suitable substituents;

R^4 and R^6 are each independently H or C_1 - C_4 alkyl;

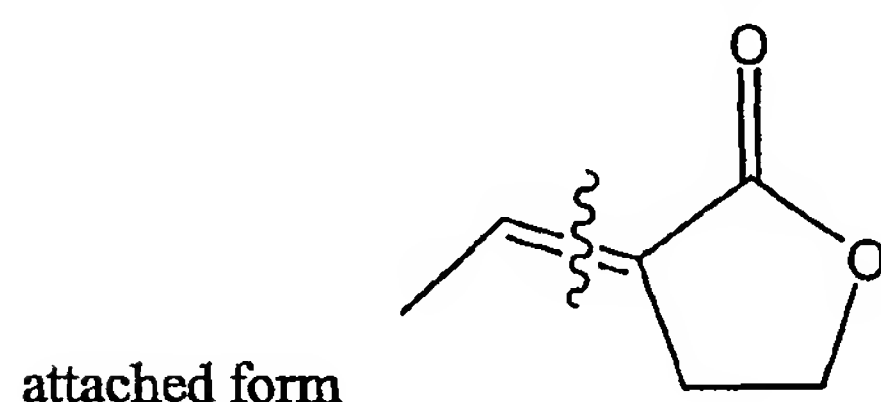
R^5 is H, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl or an arylalkyl, heteroarylalkyl, cycloalkylalkyl group or a straight-chain saturated hydrocarbon moiety or an unsaturated hydrocarbon moiety, where the arylalkyl, heteroarylalkyl, cycloalkylalkyl group is unsubstituted or substituted with one or more suitable substituents;

R^7 is selected from $-CH_2CH_2C(O)NH_2$; $-CH_2CH_2C(O)NH$ -alkyl;

- 189 -



Z¹ is H or C₁-C₄ alkyl and Z is -CO₂-alkyl, -CO₂-cycloalkyl, -CO₂-alkylaryl or -CO₂-alkylheterocycloaryl, or Z¹ and Z taken together with the atom to which they are



68. The compound according to claim 67, wherein:

R¹ is H, halo, C₁-C₄ alkyl, C₁-C₄ haloalkyl or a phenyl, naphthyl, isoxazolyl, pyridyl, quinoyl or isoquinoyl group, where the phenyl, naphthyl, isoxazolyl, pyridyl, quinoyl or isoquinoyl group is unsubstituted or substituted with one or more substituents independently selected from: halo, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy and methylenedioxy;

R² and R³ are each H; or

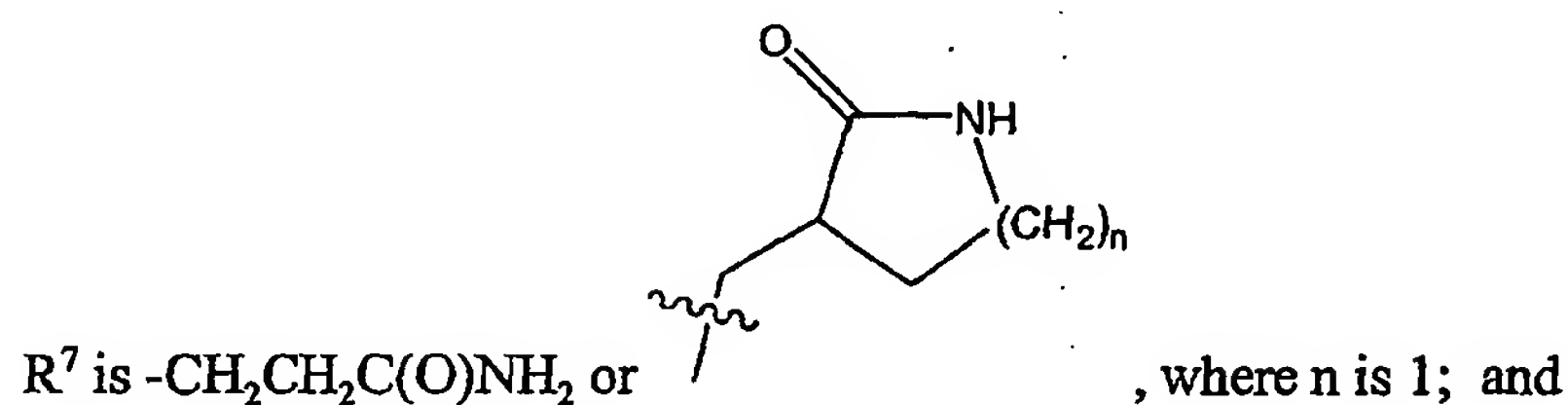
R¹ together with R² form a phenyl ring, which is unsubstituted or substituted with one or more suitable substituents and R³ is H;

R⁴ and R⁶ are each H;

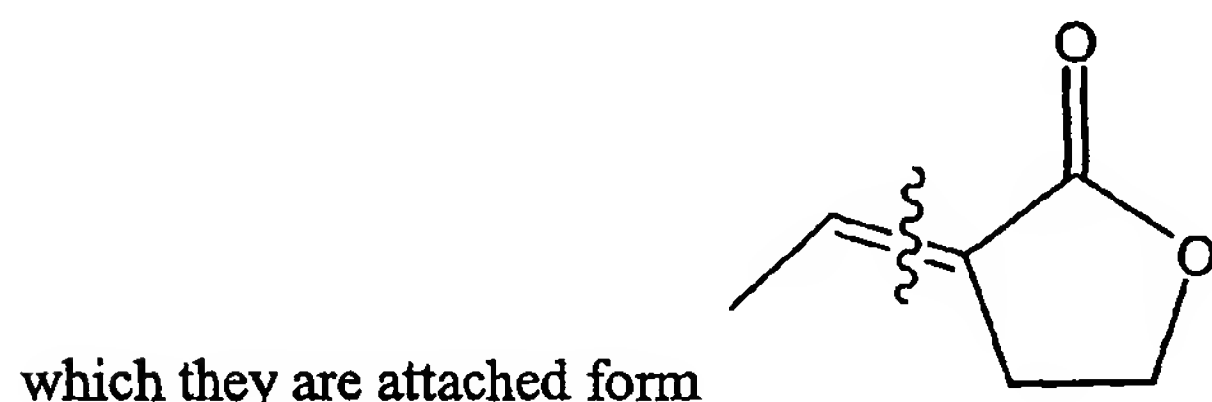
R⁵ is H or substituted or unsubstituted methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, -methylcyclohexyl, -methylthienyl or benzyl, where the substituted methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, and -methylcyclohexyl is substituted by one or more substituents independently selected from halo, alkoxy, aryloxy, alkylthio and arylthio; the substituted thienyl is substituted by one or more substituents independently selected from lower alkyl, lower alkoxy, hydroxy, amino, alkylamino, dialkylamino and halo; and the phenyl moiety of the substituted benzyl is substituted by one or more substituents independently selected

- 190 -

from lower alkyl, lower alkoxy, alkylendioxy, hydroxy, amino, alkylamino, dialkylamino and halo;



Z^1 is H and Z is $-\text{CO}_2\text{CH}_2\text{CH}_3$, $-\text{CO}_2(\text{CH}(\text{CH}_3)_2)$, $-\text{CO}_2(\text{C}(\text{CH}_3)_3)$, $-\text{CO}_2\text{CH}_2(\text{C}(\text{CH}_3)_3)$, $-\text{CO}_2(\text{cyclo-C}_5\text{H}_9)$ or Z^1 and Z taken together with the atom to



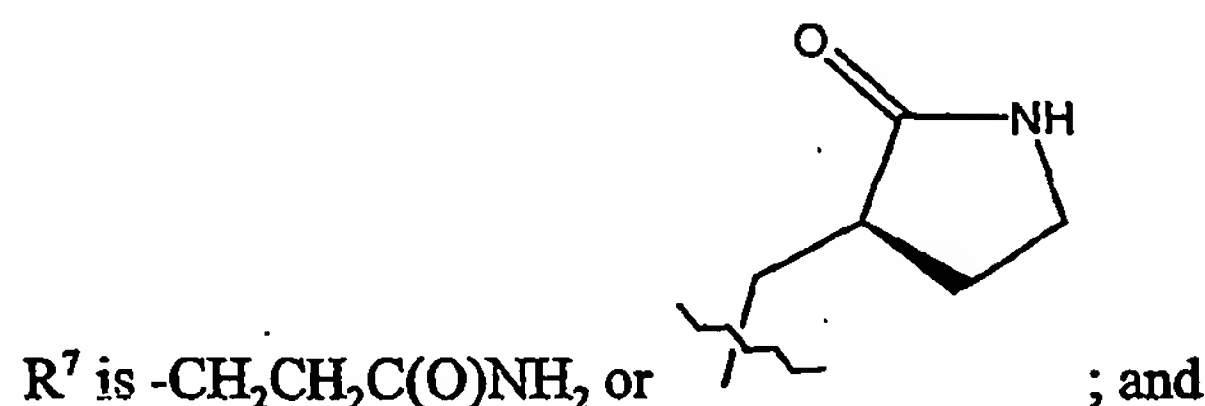
69. The compound according to claim 67, wherein:

R^1 is H, phenyl, α -naphthyl, β -naphthyl, 2-chlorophenyl, 2- α,α,α -trifluoromethylphenyl, 3-chloro-6-methoxyphenyl, 2,3-dichlorophenyl, 4-isoquinoyl, 3-iso-propylphenyl, 2,5-dimethoxyphenyl, 2-methoxyphenyl, 2-methylphenyl, 2-bromophenyl, 3-pyridyl, 4-pyridyl, 3-methyl-isoxazol-5-yl, 3,3,3-trifluoroprop-1-yl, or 2,3-benzo[d]dioxolyl;

R^2 and R^3 are each H;

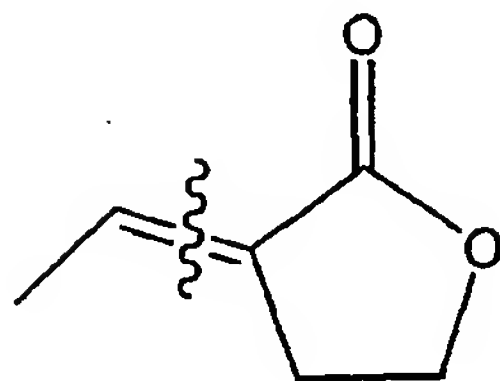
R^4 and R^6 are each H;

R^5 is H, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, -methylcyclohexyl, benzyl or substituted benzyl, wherein the phenyl moiety of the substituted benzyl comprises one or more substituents independently selected from C_1 - C_4 alkyl, C_1 - C_4 alkoxy and halo;



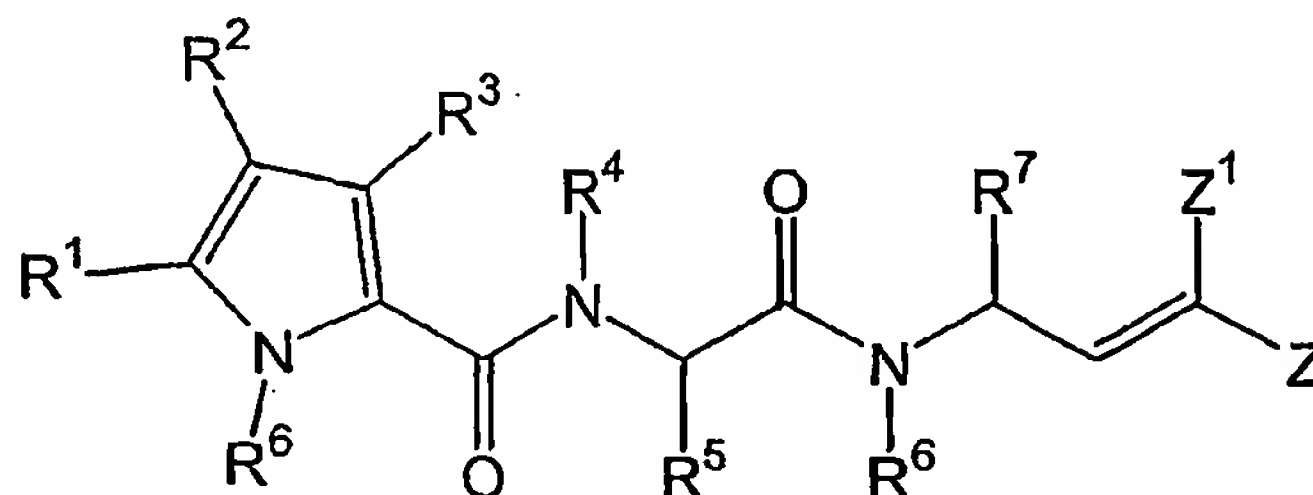
- 191 -

Z^1 is H and Z is $-\text{CO}_2\text{CH}_2\text{CH}_3$ or Z^1 and Z taken together with the atom to which



they are attached form

70. An antipicornaviral compound having the formula:



wherein:

R^1 is H, halo, $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_1\text{-C}_4$ haloalkyl, or an aryl or heteroaryl group, where the aryl or heteroaryl group is unsubstituted or substituted with one or more suitable substituents;

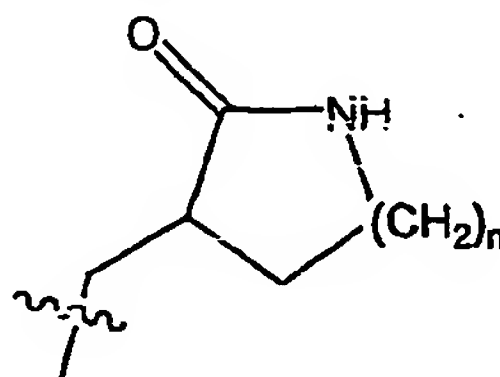
R^2 and R^3 are each independently H or $\text{C}_1\text{-C}_4$ alkyl; or

or R^1 together with R^2 form a cycloalkyl, heterocycloalkyl, aryl or heteroaryl ring, where the cycloalkyl, heterocycloalkyl, aryl or heteroaryl ring is unsubstituted or substituted with one or more suitable substituents;

R^4 and R^6 are each independently H or $\text{C}_1\text{-C}_4$ alkyl;

R^5 is H, $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_1\text{-C}_4$ haloalkyl or an arylalkyl, heteroarylalkyl, cycloalkylalkyl group or a straight-chain saturated hydrocarbon moiety or an unsaturated hydrocarbon moiety, where the arylalkyl, heteroarylalkyl, cycloalkylalkyl group is unsubstituted or substituted with one or more suitable substituents;

R^7 is selected from $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$; $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH-alkyl}$;

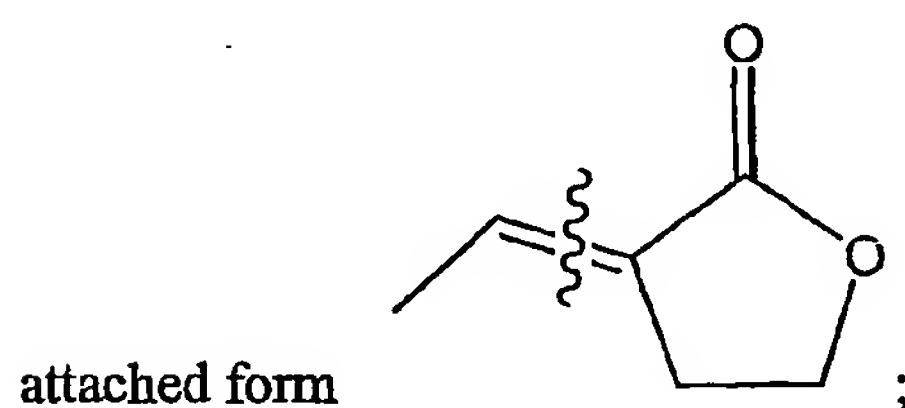


$-\text{CH}_2\text{NHC}(\text{O})\text{CH}_3$; and

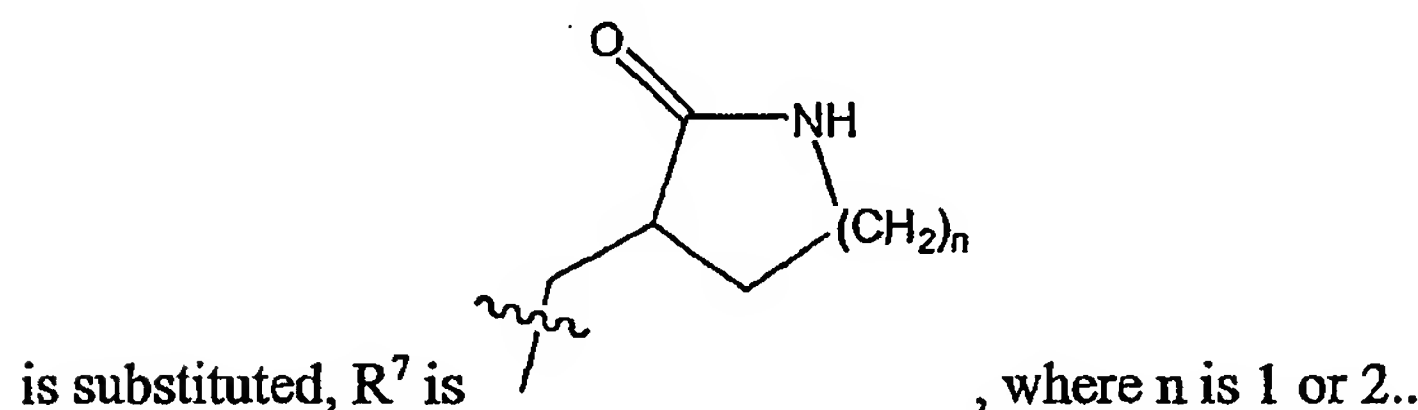
, where n is 1 or 2; and

- 192 -

Z^1 is H or C_1 - C_4 alkyl and Z is $-\text{CO}_2$ -alkyl, $-\text{CO}_2$ -cycloalkyl, $-\text{CO}_2$ -alkylaryl or $-\text{CO}_2$ -alkylheterocycloaryl, or Z^1 and Z taken together with the atom to which they are



provided that when R^1 together with R^2 form a phenyl ring and the phenyl ring



71. The compound according to claim 70, wherein:

R^1 is H, halo, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl or a phenyl, naphthyl, isoxazolyl, pyridyl, quinoyl or isoquinoyl group, where the phenyl, naphthyl, isoxazolyl, pyridyl, quinoyl or isoquinoyl group is unsubstituted or substituted with one or more substituents independently selected from halo, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy and methylenedioxy;

R^2 and R^3 are each H; or

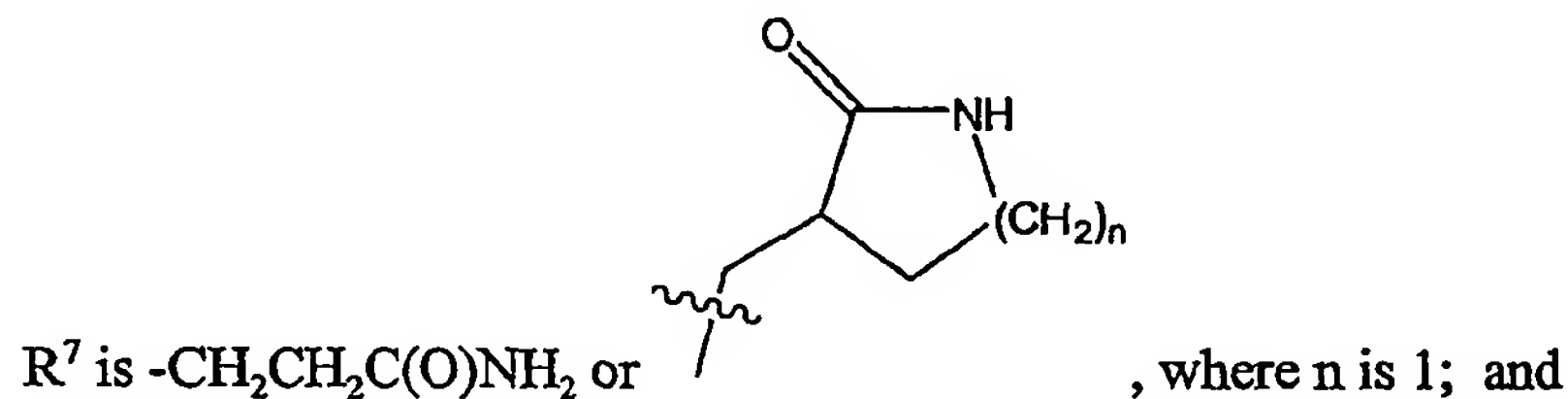
R^1 together with R^2 form an unsubstituted phenyl ring and R^3 is H;

R^4 and R^6 are each H;

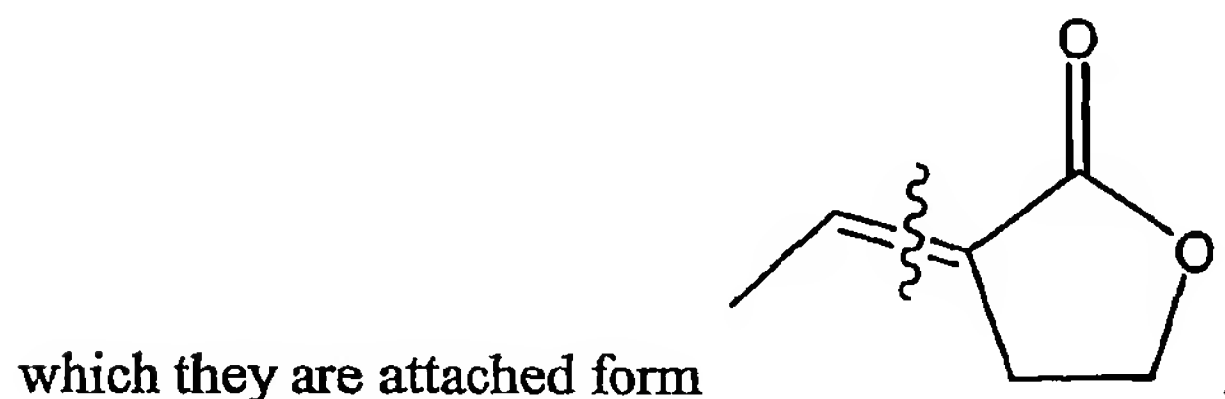
R^5 is H or substituted or unsubstituted methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, -methylcyclohexyl, -methylthienyl or benzyl, where the substituted methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, and -methylcyclohexyl is substituted by one or more substituents independently selected from halo, alkoxy, aryloxy, alkylthio and arylthio; the substituted thienyl is substituted by one or more substituents independently selected from lower alkyl, lower alkoxy, hydroxy, amino, alkylamino, dialkylamino and halo; and the phenyl moiety of the

- 193 -

substituted benzyl is substituted by one or more substituents independently selected from lower alkyl, lower alkoxy, alkylendioxy, hydroxy, amino, alkylamino, dialkylamino and halo;



Z^1 is H and Z is $-\text{CO}_2\text{CH}_2\text{CH}_3$, $-\text{CO}_2(\text{CH}(\text{CH}_3)_2)$, $-\text{CO}_2(\text{C}(\text{CH}_3)_3)$, $-\text{CO}_2\text{CH}_2(\text{C}(\text{CH}_3)_3)$, $-\text{CO}_2(\text{cyclo-C}_5\text{H}_9)$ or Z^1 and Z taken together with the atom to



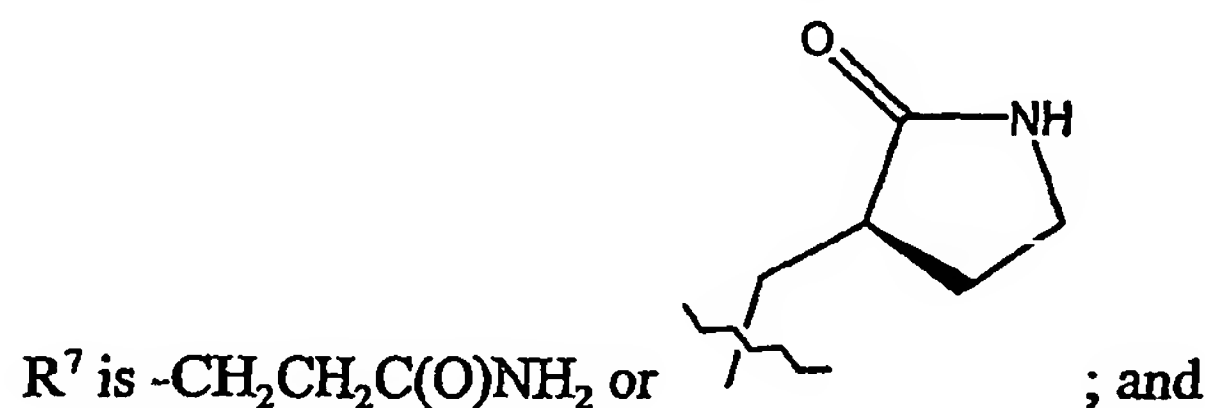
72. The compound according to claim 70, wherein:

R^1 is H, phenyl, α -naphthyl, β -naphthyl, 2-chlorophenyl, 2- α,α,α -trifluoromethylphenyl, 3-chloro-6-methoxyphenyl, 2,3-dichlorophenyl, 4-isoquinoyl, 3-iso-propylphenyl, 2,5-dimethoxyphenyl, 2-methoxyphenyl, 2-methylphenyl, 2-bromophenyl, 3-pyridyl, 4-pyridyl, 3-methyl-isoxazol-5-yl, 3,3,3-trifluoroprop-1-yl, or 2,3-benzo[d]dioxolyl;

R^2 and R^3 are each H;

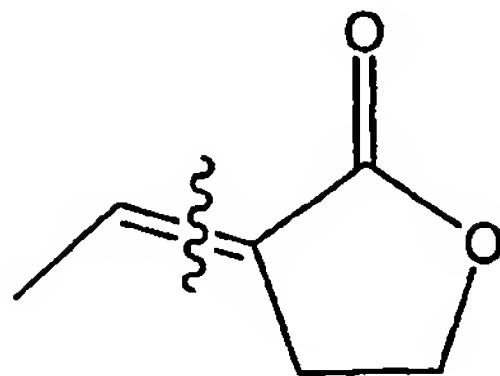
R^4 and R^6 are each H;

R^5 is H, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, -methylcyclohexyl, benzyl or substituted benzyl, wherein the phenyl moiety of the substituted benzyl comprises one or more substituents independently selected from C_1 - C_4 alkyl, C_1 - C_4 alkoxy and halo;



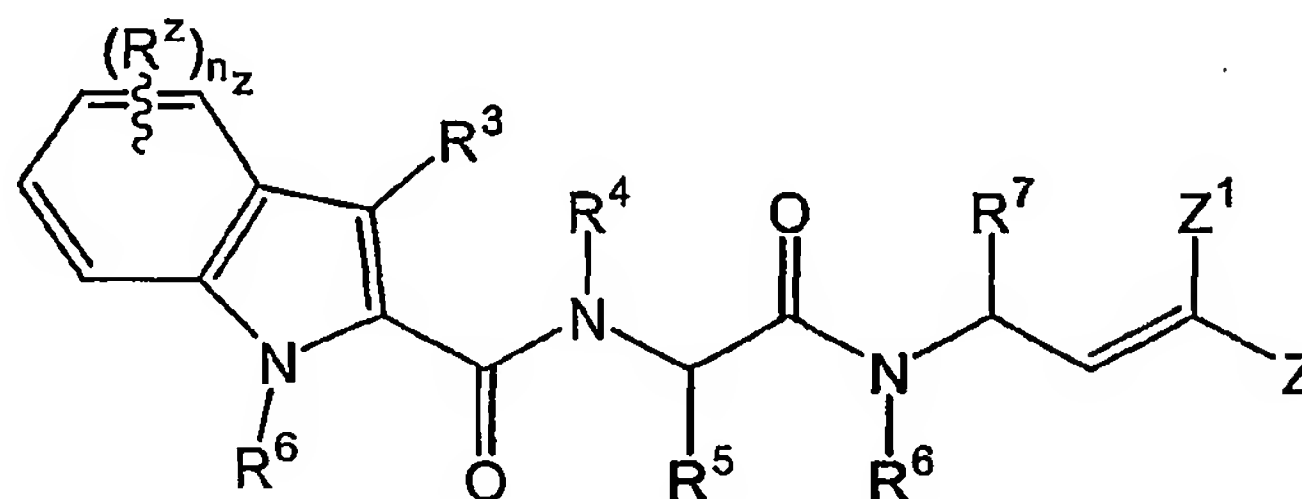
- 194 -

Z^1 is H and Z is $-\text{CO}_2\text{CH}_2\text{CH}_3$ or Z^1 and Z taken together with the atom to which



they are attached form

73. An antipicornaviral compound having the formula:



wherein:

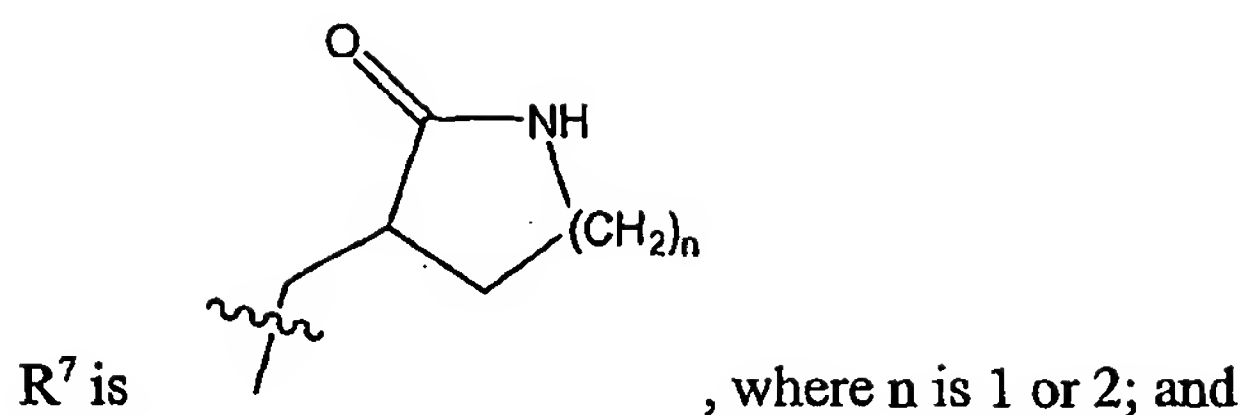
each R^Z is independently selected from halo and a $\text{C}_1\text{-C}_4$ alkoxy, $\text{C}_1\text{-C}_4$ alkyl, aryl, heterocycloalkyl or heteroaryl group where the $\text{C}_1\text{-C}_4$ alkoxy or $\text{C}_1\text{-C}_4$ alkyl group is unsubstituted or substituted with one or more substituents independently selected from halo, $\text{C}_1\text{-C}_4$ alkoxy or $\text{C}_1\text{-C}_4$ haloalkoxy and the aryl, heterocycloalkyl or heteroaryl group is unsubstituted or substituted by one or more substituents independently selected from halo, $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_1\text{-C}_4$ haloalkyl, $\text{C}_1\text{-C}_4$ alkoxy, $\text{C}_1\text{-C}_4$ haloalkoxy and methylenedioxy or two R^Z at adjacent positions are methylenedioxy; and n_Z is an integer from 1 to 4;

R^3 is H, halo, $\text{C}_1\text{-C}_4$ alkoxy, unsubstituted $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_1\text{-C}_4$ haloalkyl and $\text{C}_1\text{-C}_4$ alkoxyalkyl;

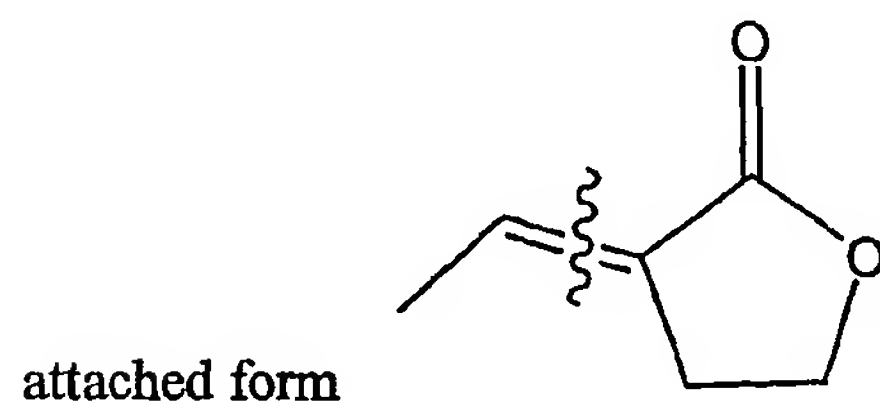
R^4 and R^6 are each independently H or $\text{C}_1\text{-C}_4$ alkyl;

R^5 is H, $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_1\text{-C}_4$ haloalkyl or an arylalkyl, heteroarylalkyl, cycloalkylalkyl group or a straight-chain saturated hydrocarbon moiety or an unsaturated hydrocarbon moiety, where the arylalkyl, heteroarylalkyl, cycloalkylalkyl group is unsubstituted or substituted with one or more suitable substituents;

- 195 -

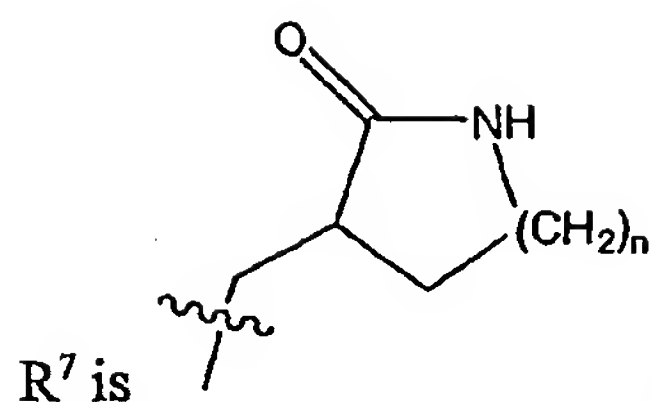


Z¹ is H or C₁-C₄ alkyl and Z is -CO₂-alkyl, -CO₂-cycloalkyl, -CO₂-alkylaryl or -CO₂-alkylheterocycloaryl, or Z¹ and Z taken together with the atom to which they are



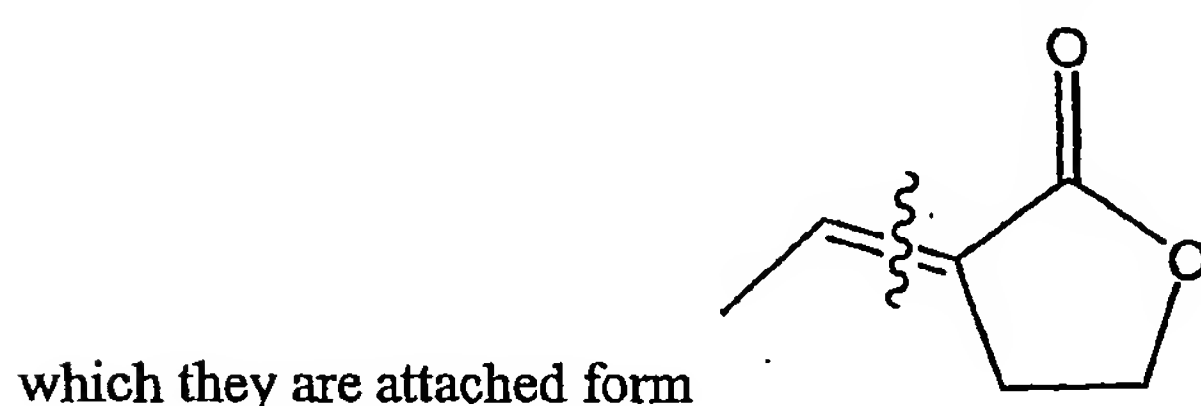
74. The compound according to claim 73, wherein
- each R^z is independently selected from halo, C₁-C₄ alkoxy, unsubstituted C₁-C₄ alkyl, C₁-C₄ haloalkyl, and C₁-C₄ alkoxyalkyl and n₂ is an integer from 1 to 2;
 - R³ is H or C₁-C₄ alkyl;
 - R⁴ and R⁶ are each H;
 - R⁵ is H or substituted or unsubstituted methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, -methylcyclohexyl, -methylthienyl or benzyl, where the substituted methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, and -methylcyclohexyl is substituted by one or more substituents independently selected from halo, alkoxy, aryloxy, alkylthio and arylthio; the substituted thienyl is substituted by one or more substituents independently selected from lower alkyl, lower alkoxy, hydroxy, amino, alkylamino, dialkylamino and halo; and the phenyl moiety of the substituted benzyl is substituted by one or more substituents independently selected from lower alkyl, lower alkoxy, alkylenedioxy, hydroxy, amino, alkylamino, dialkylamino and halo;

- 196 -

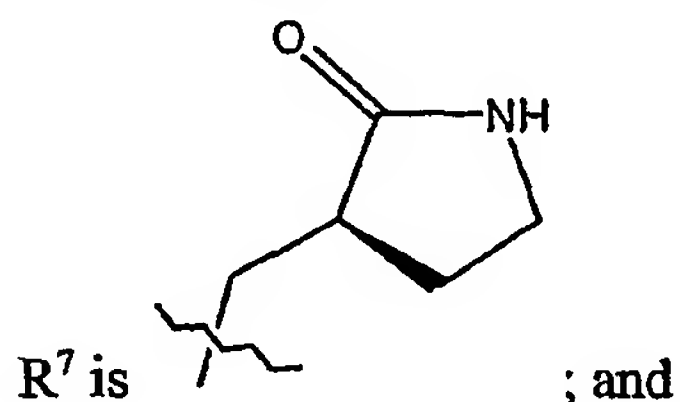


where n is 1; and

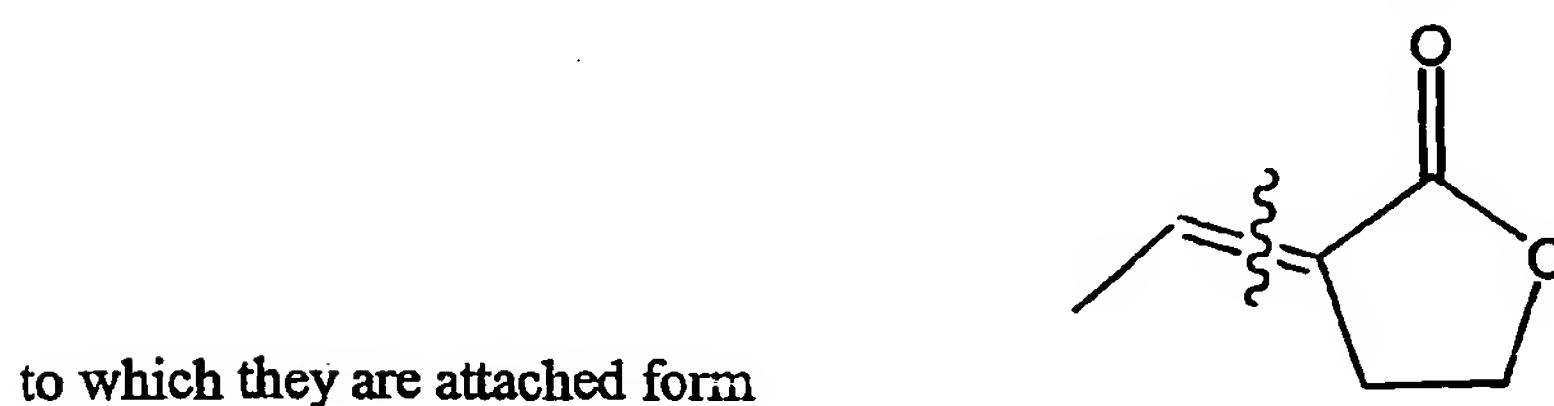
Z¹ is H and Z is -CO₂CH₂CH₃, -CO₂(CH(CH₃)₂), -CO₂(C(CH₃)₃),
-CO₂CH₂(C(CH₃)₃), -CO₂(cyclo-C₅H₉) or Z¹ and Z taken together with the atom to



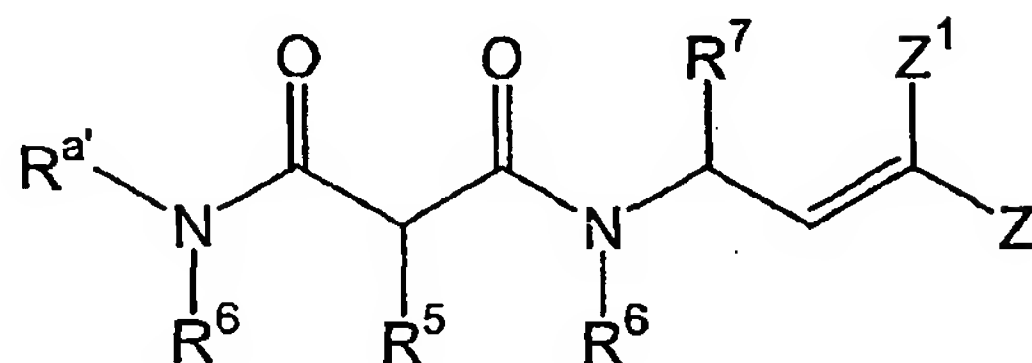
75. The compound according to claim 73, wherein
each R^z is independently selected from halo, C₁-C₄ alkoxy, unsubstituted
C₁-C₄ alkyl and C₁-C₄ haloalkyl, and n_z is 1 or 2;
R³ is H;
R⁴ and R⁶ are each H;
R⁵ is H, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl,
2-propen-2-yl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, -methylcyclohexyl, benzyl or
substituted benzyl, wherein the phenyl moiety of the substituted benzyl comprises one
or more substituents independently selected from C₁-C₄ alkyl, C₁-C₄ alkoxy and halo;



Z¹ is H and Z is -CO₂CH₂CH₃ or Z¹ and Z taken together with the atom



76. An antipicornaviral compound having the formula:



wherein:

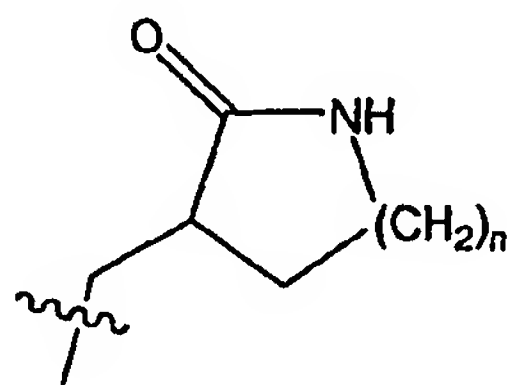
R^a is a C_1 - C_4 alkyl, aryl, C_3 - C_7 cycloalkyl, heterocycloalkyl or heteroaryl group, where the C_1 - C_4 alkyl, aryl, C_3 - C_7 cycloalkyl, heterocycloalkyl or heteroaryl group is unsubstituted or substituted with one or more substituents independently selected from alkyl, haloalkyl, alkylendioxy, nitro, amino, hydroxamino, alkylamino, dialkylamino, halo, hydroxyl, alkoxy, haloalkoxy, aryloxy, mercapto, alkylthio or arylthio, aryl or heteroaryl, where the aryl or heteroaryl group is unsubstituted or substituted with one or more substituents independently selected from halo, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy and methylenedioxy;

each R^6 is independently H or C_1 - C_4 alkyl;

R^5 is H, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl or an arylalkyl, heteroarylalkyl, cycloalkylalkyl group or a straight-chain saturated hydrocarbon moiety or an unsaturated hydrocarbon moiety, where the arylalkyl, heteroarylalkyl, cycloalkylalkyl group is unsubstituted or substituted with one or more suitable substituents;

R^7 is selected from $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$; $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH-alkyl}$;

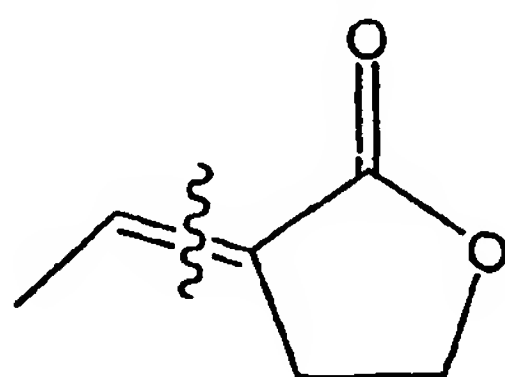
$-\text{CH}_2\text{NHC}(\text{O})\text{CH}_3$; and



, where n is 1 or 2; and

Z^1 is H or C_1 - C_4 alkyl and Z is $-\text{CO}_2$ -alkyl, $-\text{CO}_2$ -cycloalkyl, $-\text{CO}_2$ -alkylaryl or $-\text{CO}_2$ -alkylheterocycloaryl, or Z^1 and Z taken together with the atom to which they are

attached form

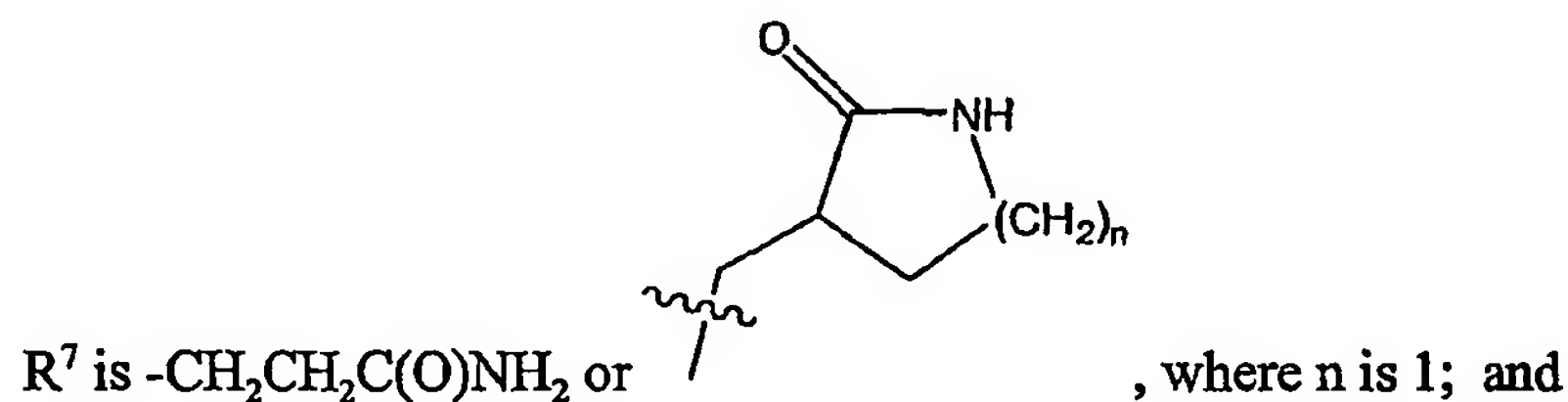


77. The compound according to claim 76, wherein:

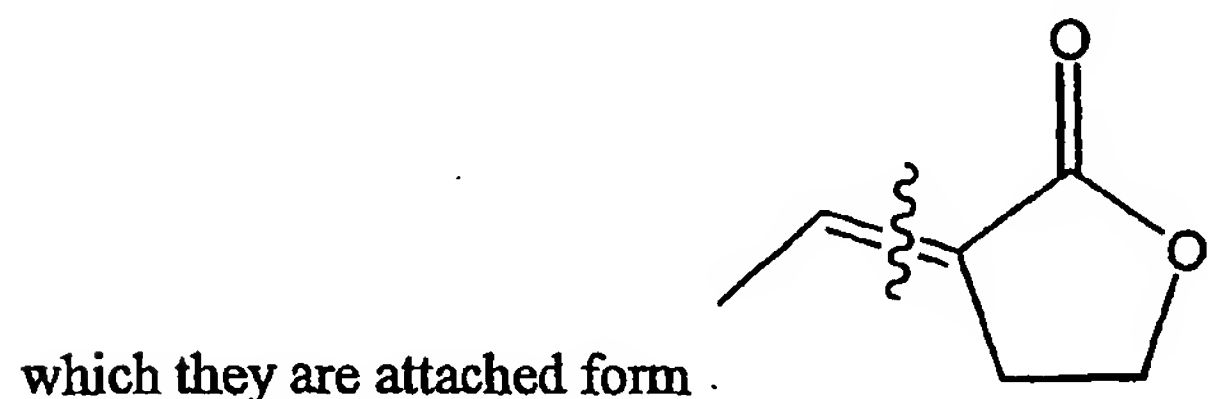
R^a is a C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, phenyl, naphthyl, C_5 - C_6 cycloalkyl, isoquinoyl, pyridyl or pyrrolyl group, where the phenyl, naphthyl, isoquinoyl, pyridyl or pyrrolyl group is unsubstituted or substituted with one or more substituents independently selected from halo, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy and methylenedioxy;

each R^6 is H;

R^5 is H or substituted or unsubstituted methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, -methylcyclohexyl, -methylthienyl or benzyl, where the substituted methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, and -methylcyclohexyl is substituted by one or more substituents independently selected from halo, alkoxy, aryloxy, alkylthio and arylthio; the substituted thienyl is substituted by one or more substituents independently selected from lower alkyl, lower alkoxy, hydroxy, amino, alkylamino, dialkylamino and halo; and the phenyl moiety of the substituted benzyl is substituted by one or more substituents independently selected from lower alkyl, lower alkoxy, alkylenedioxy, hydroxy, amino, alkylamino, dialkylamino and halo;



Z^1 is H and Z is $-\text{CO}_2\text{CH}_2\text{CH}_3$, $-\text{CO}_2(\text{CH}(\text{CH}_3)_2)$, $-\text{CO}_2(\text{C}(\text{CH}_3)_3)$, $-\text{CO}_2\text{CH}_2(\text{C}(\text{CH}_3)_3)$, $-\text{CO}_2(\text{cyclo-}C_5H_9)$ or Z^1 and Z taken together with the atom to



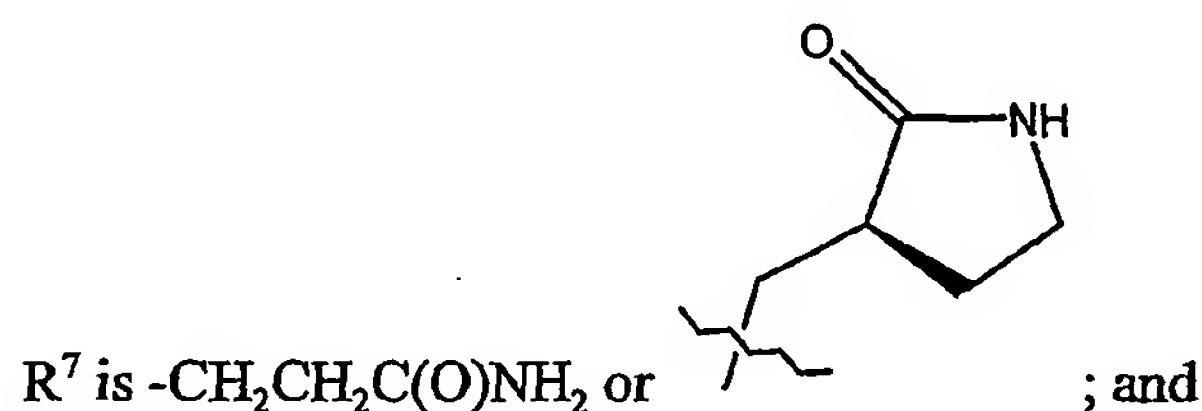
- 199 -

78. The compound according to claim 76, wherein:

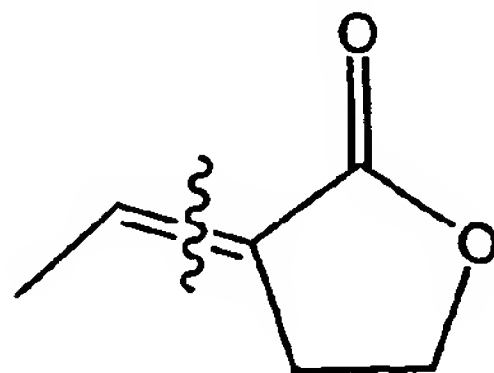
R^a is a phenyl group, where the phenyl group is unsubstituted or substituted with one or more substituents independently selected from halo, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl or C_1 - C_4 alkoxy;

each R^6 is H;

R^5 is H, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, 2-propen-1-yl, 2-propen-2-yl, 2-propyn-1-yl, 3-methyl-3-buten-1-yl, -methylcyclohexyl, benzyl or substituted benzyl, wherein the phenyl moiety of the substituted benzyl comprises one or more substituents independently selected from C_1 - C_4 alkyl, C_1 - C_4 alkoxy and halo;



Z^1 is H and Z is $-\text{CO}_2\text{CH}_2\text{CH}_3$ or Z^1 and Z taken together with the atom to which



they are attached form

79. The compound according to any one of claims 62 to 78, where R^5 is H, ethyl, 2-propyn-1-yl, methylcyclohexyl or benzyl.

80. The compound according to any one of claims 1, 8, 9, 12, 13, 14, 19, 20, 49, 62, 67, 70, 73 or 76 having antipicornaviral activity corresponding to an EC_{50} less than or equal to 100 μM in an H1-HeLa cell culture assay.

81. The compound according to claim 16, having antipicornaviral activity corresponding to an EC_{50} less than or equal to 100 μM in an H1-HeLa cell culture assay.

- 200 -

82. A pharmaceutical composition comprising:

a therapeutically effective amount of at least one antipicornaviral agent selected from compounds, prodrugs, pharmaceutically acceptable salts, pharmaceutically active metabolites, and pharmaceutically acceptable solvates defined in any one of claims 1, 8, 9, 12, 13, 14, 19, 20, 49, 62, 67, 70, 73 or 76; and

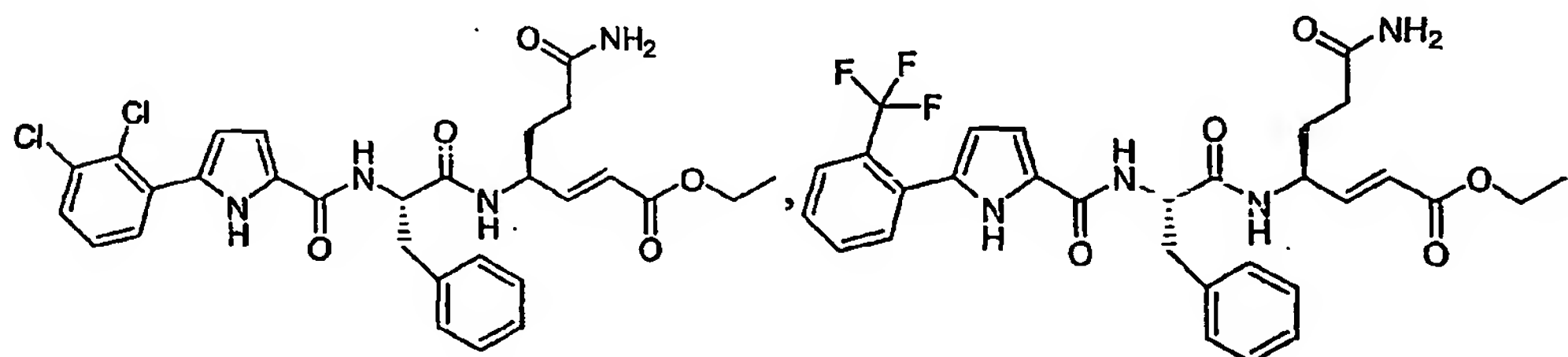
a pharmaceutically acceptable carrier, diluent, vehicle, or excipient.

83. The method of treating a mammalian disease condition mediated by picornaviral protease activity, comprising administering to a mammal in need thereof a therapeutically effective amount of at least one compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate defined in any one of claims 1, 8, 9, 12, 13, 14, 19, 20, 49, 62, 67, 70, 73 or 76.

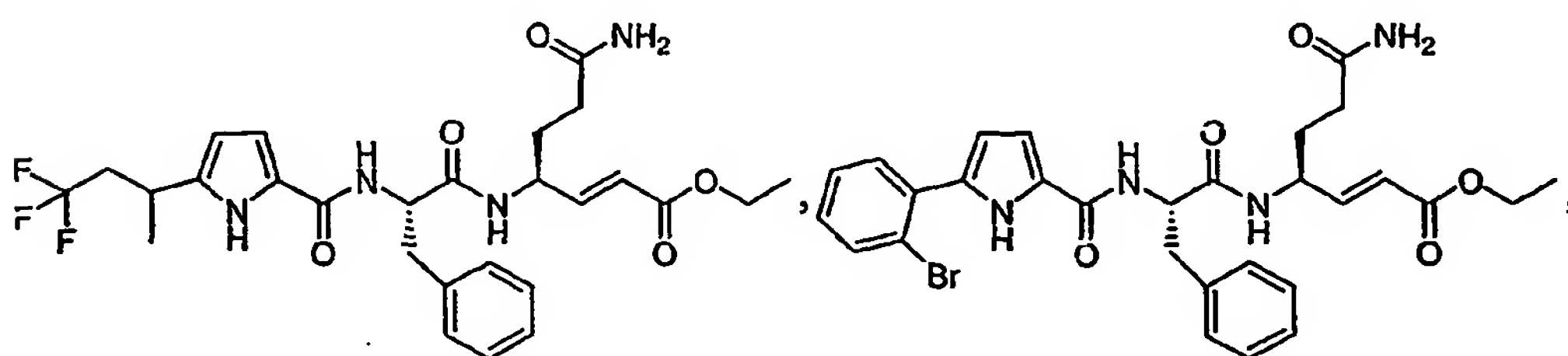
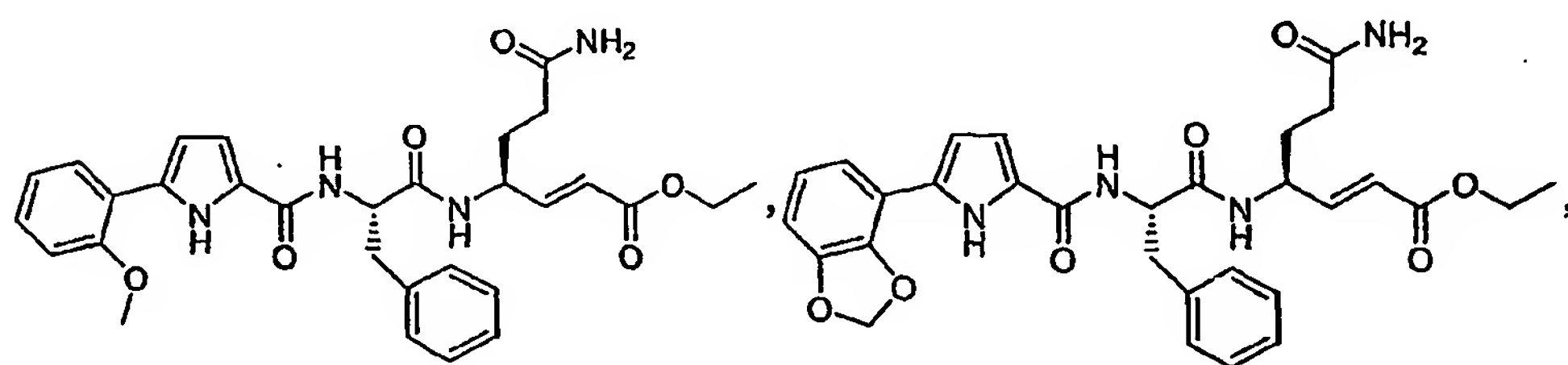
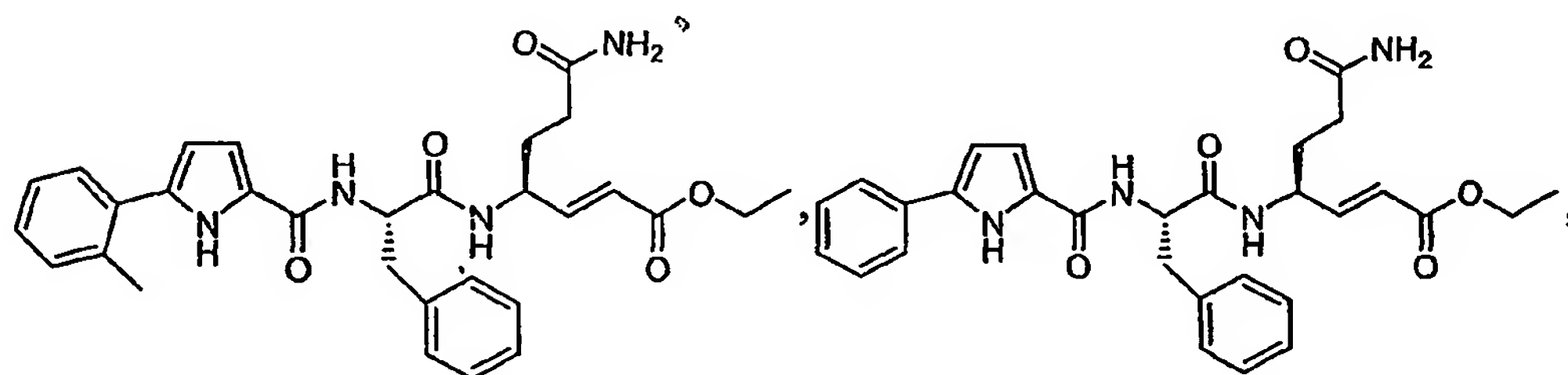
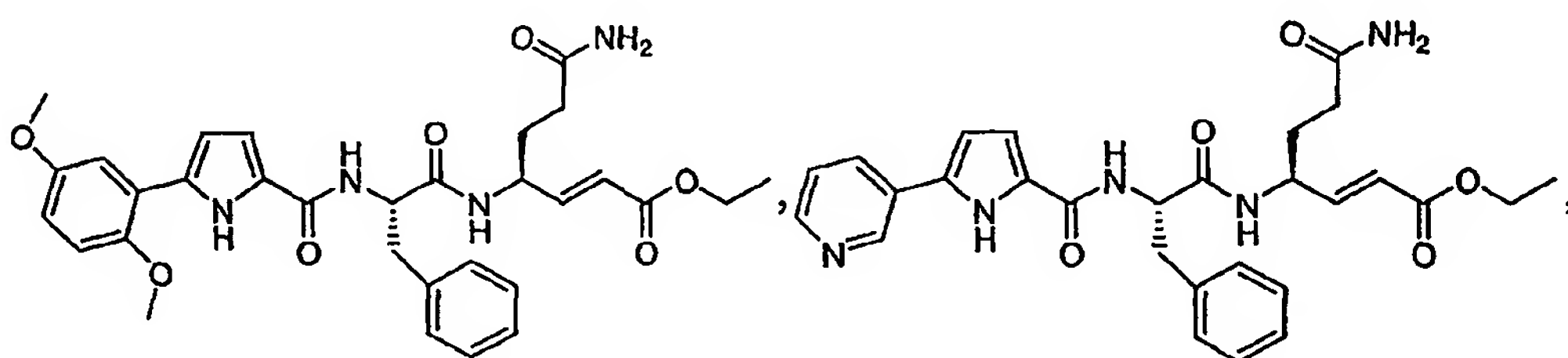
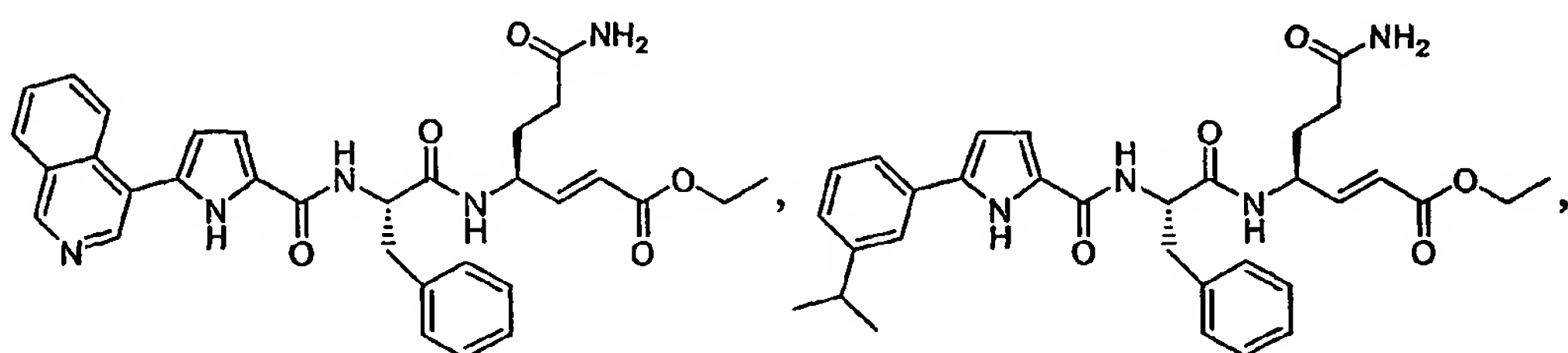
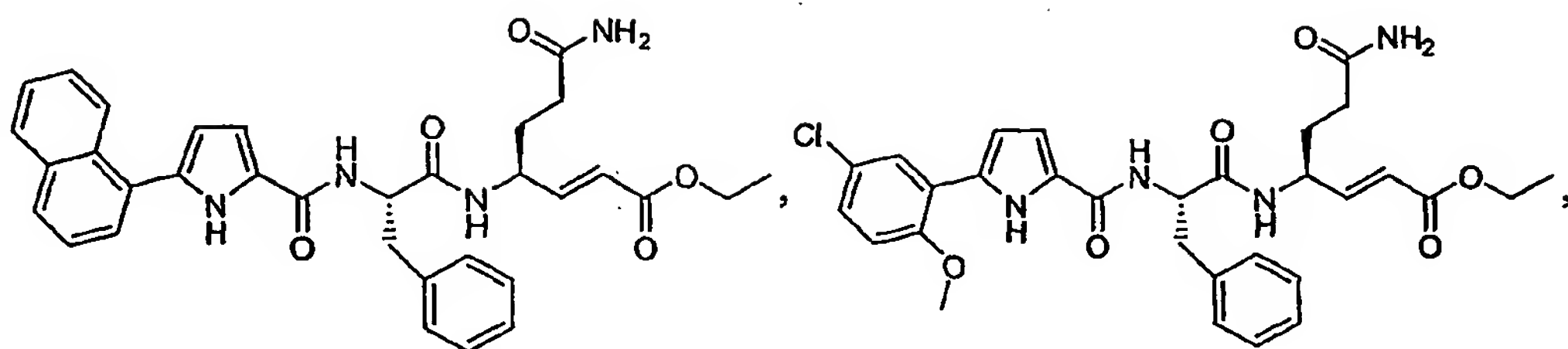
84. The method of inhibiting the activity of a picornaviral 3C protease, comprising contacting the picornaviral 3C protease with an effective amount of at least one compound, prodrug, pharmaceutically acceptable salt, pharmaceutically active metabolite, or pharmaceutically acceptable solvate defined in any one of claims 1, 8, 9, 12, 13, 14, 19, 20, 49, 62, 67, 70, 73 or 76.

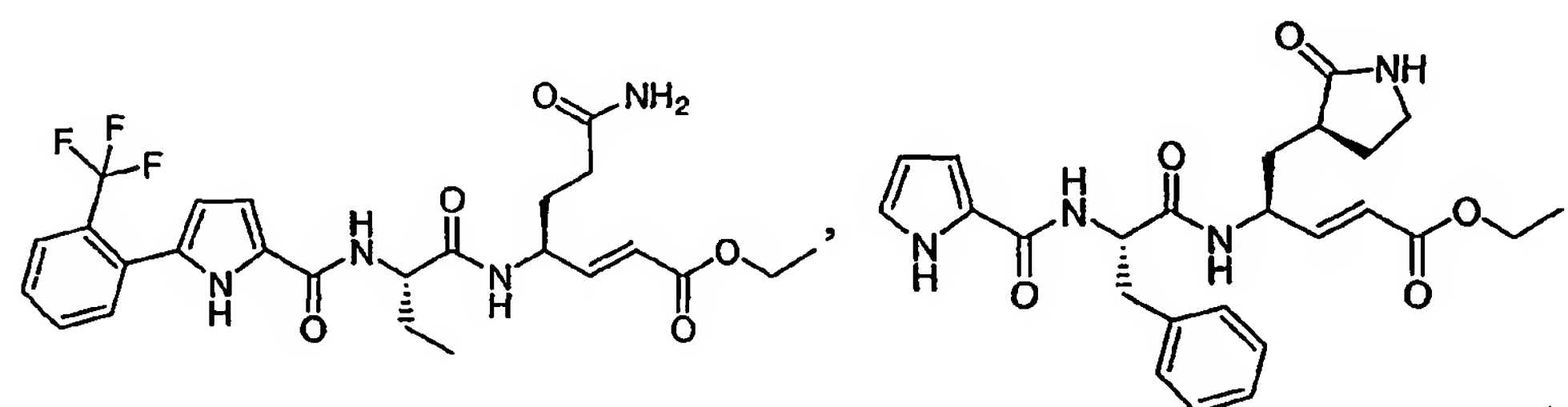
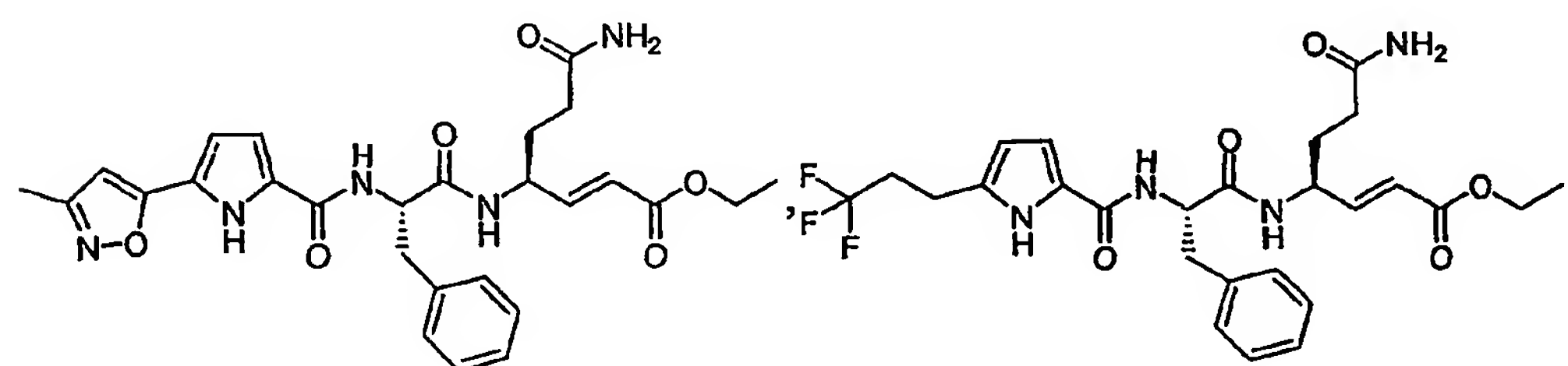
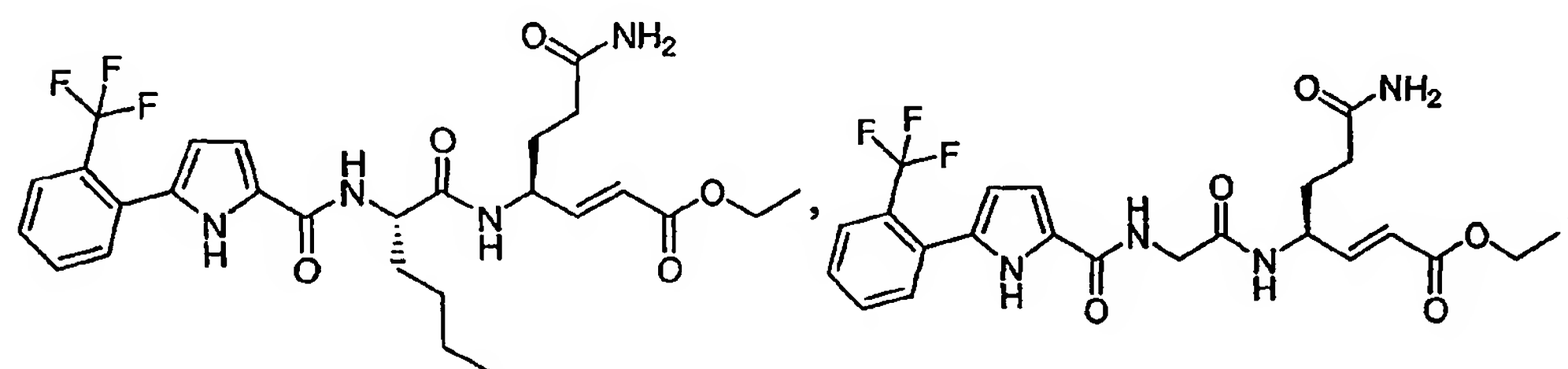
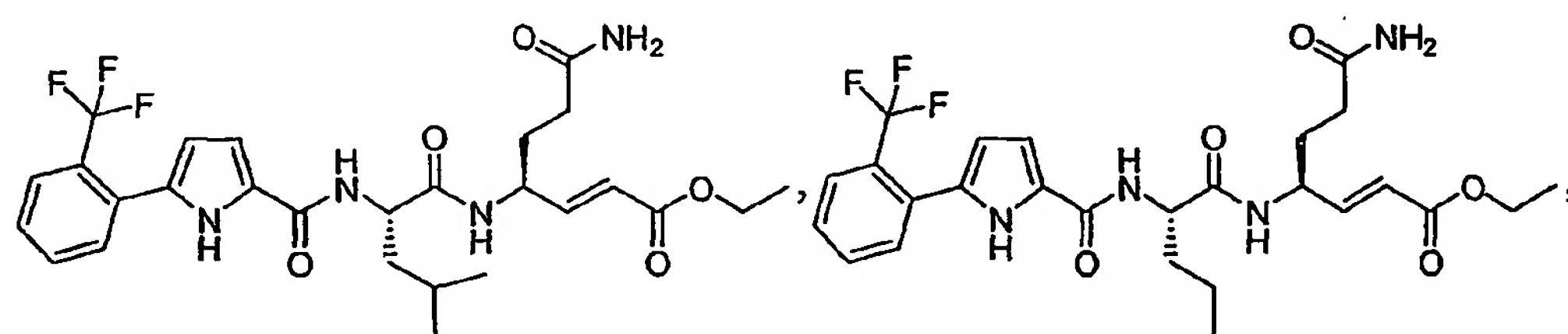
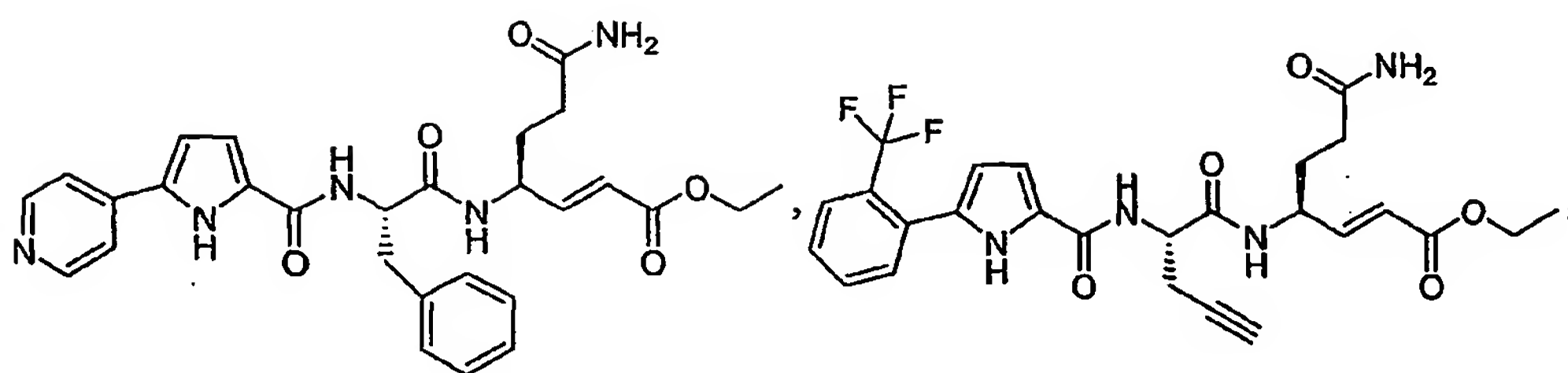
85. The method as defined in claim 53, wherein the picornaviral 3C protease is a rhinoviral protease.

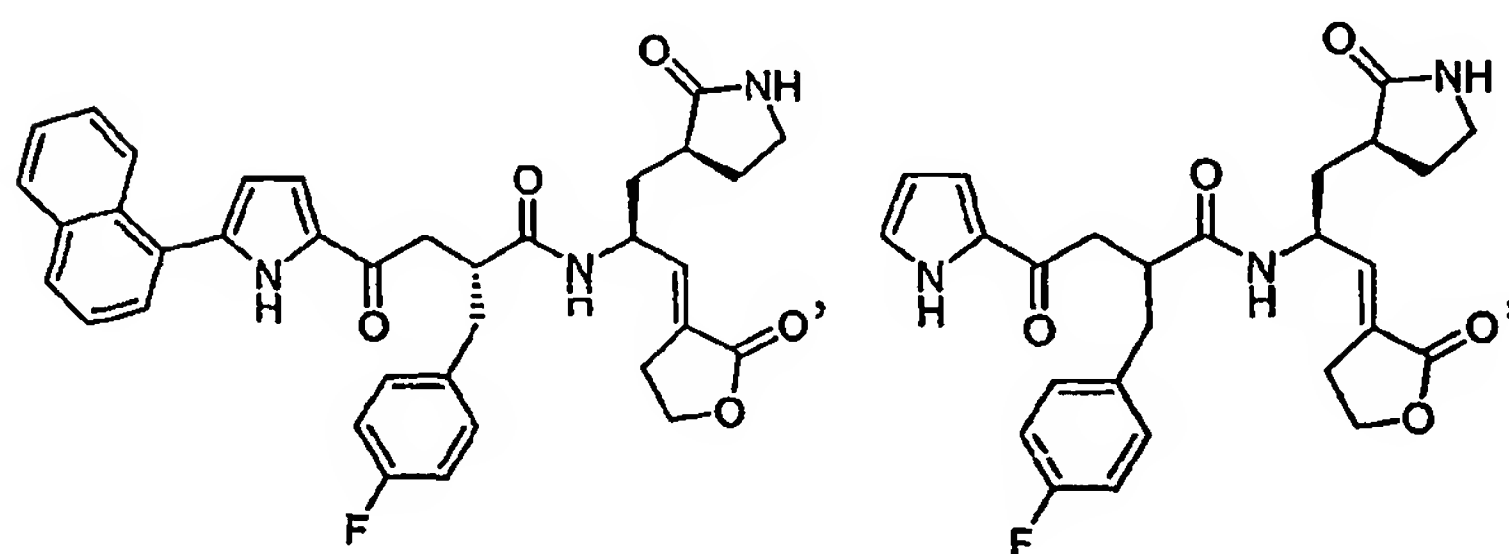
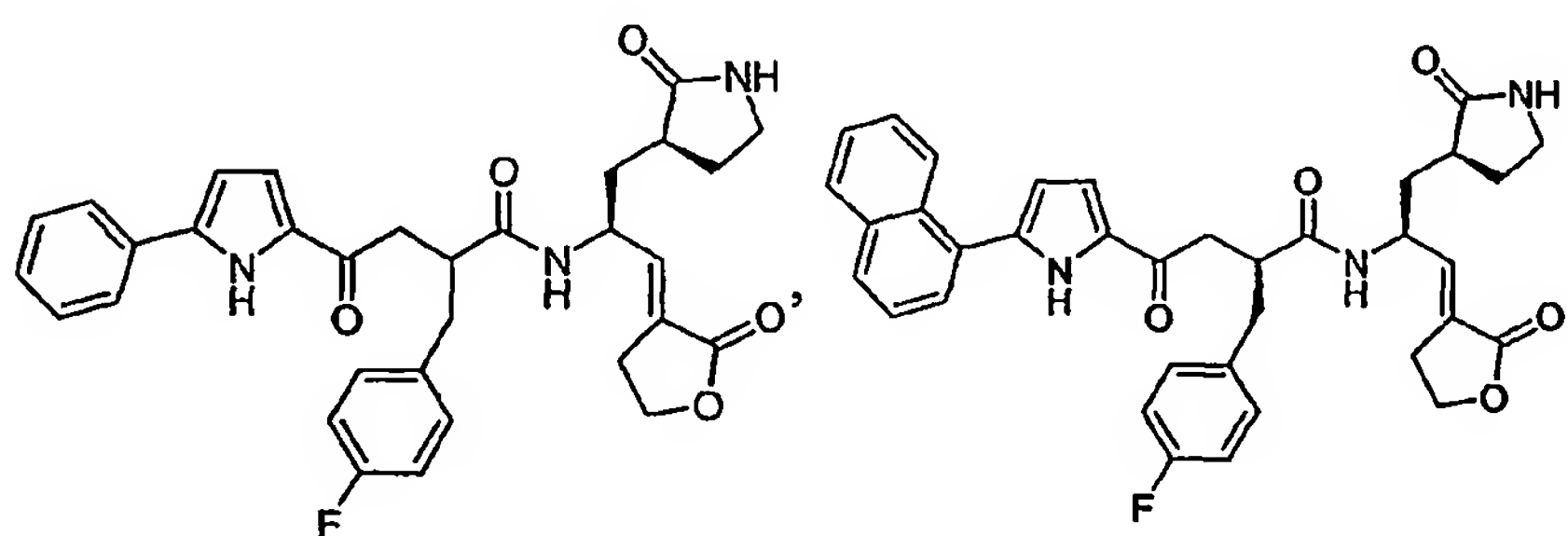
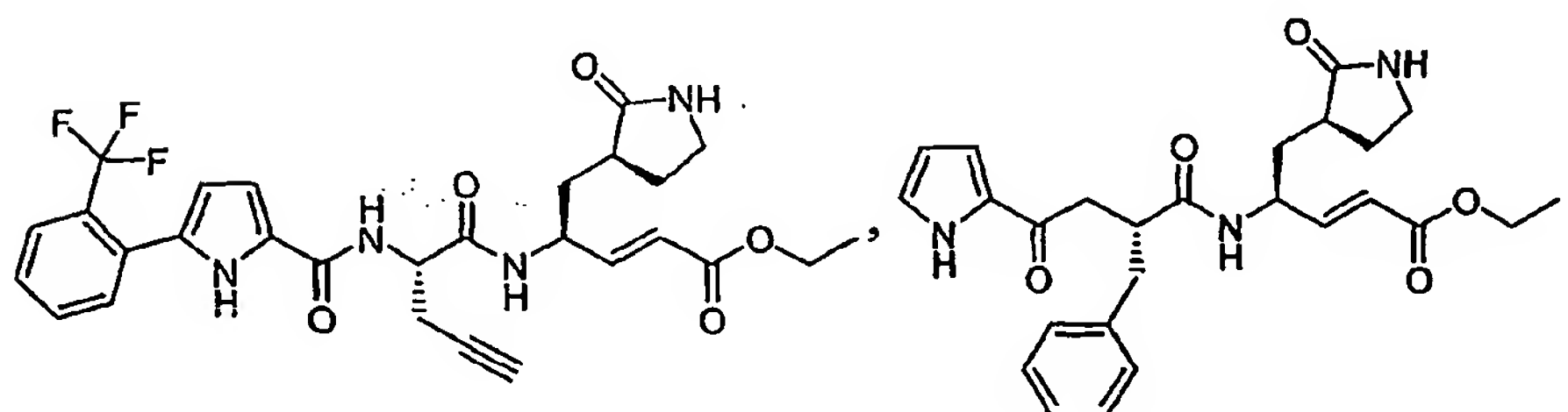
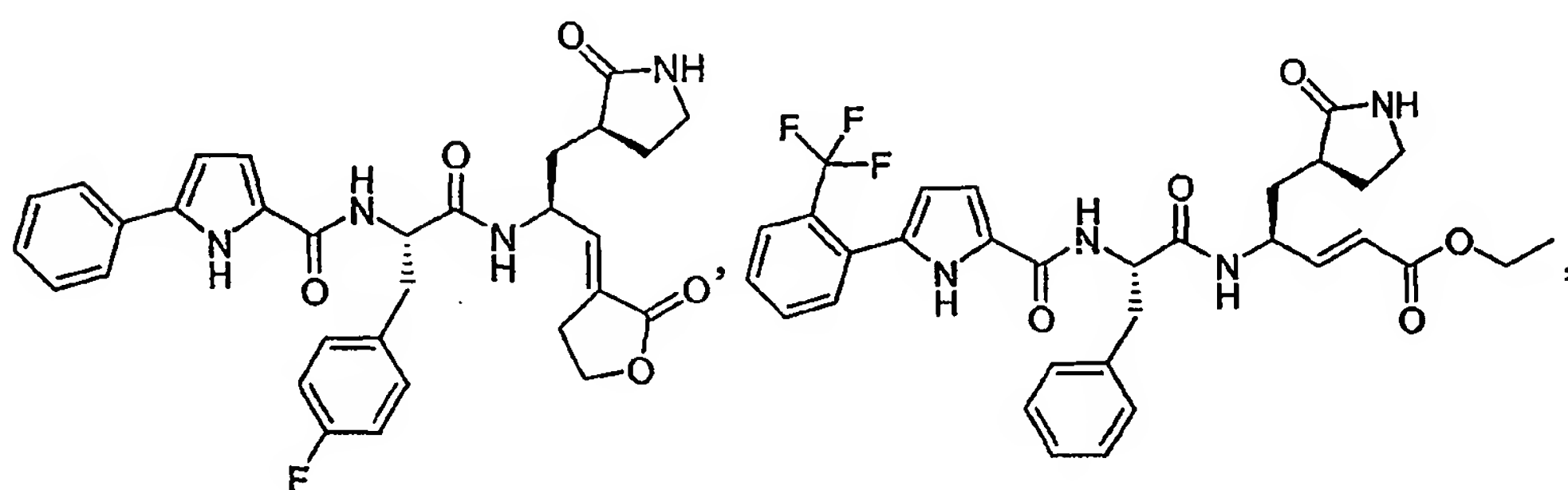
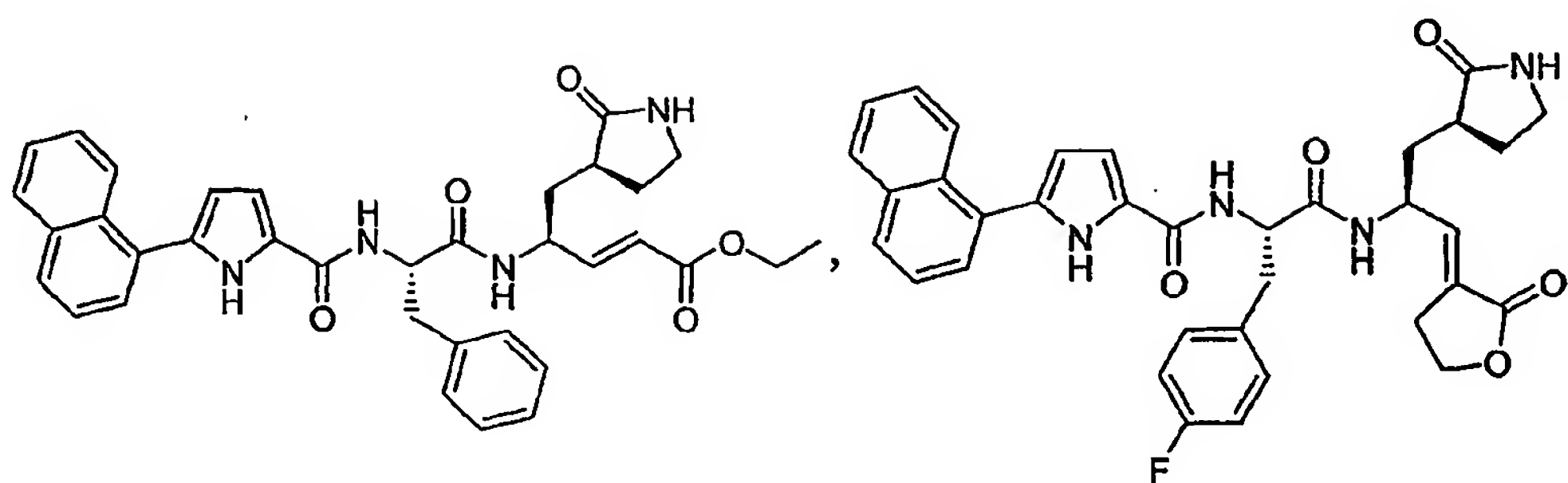
86. A compound selected from:



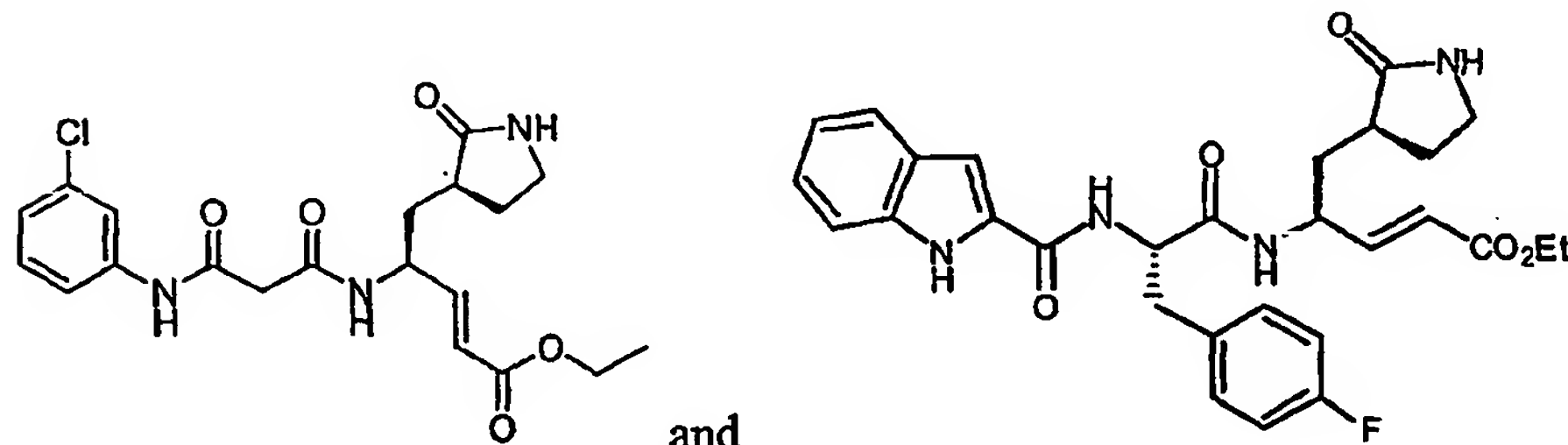
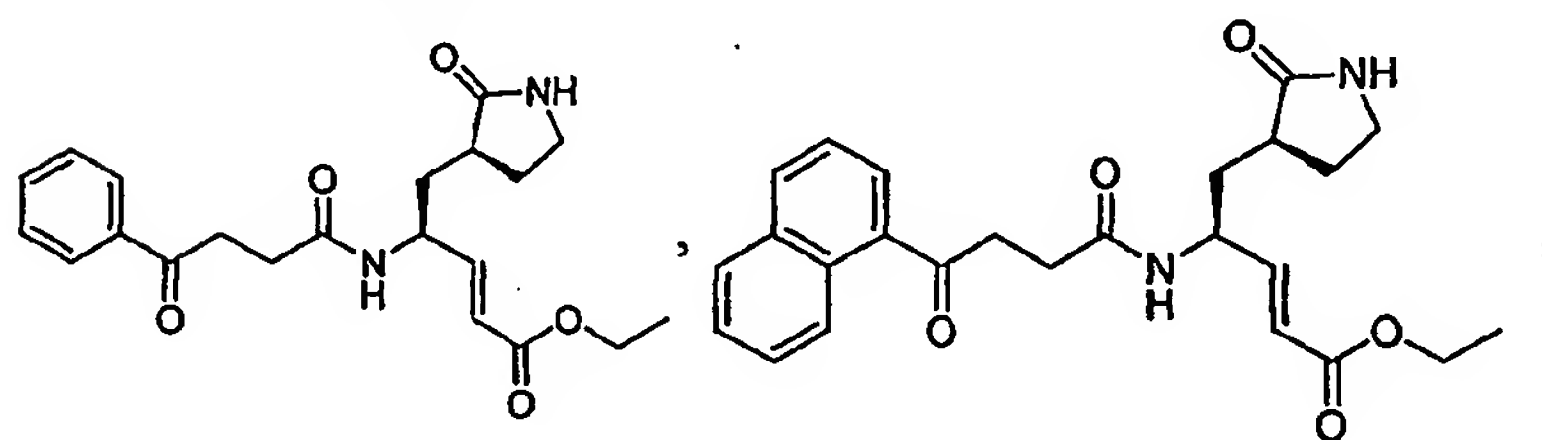
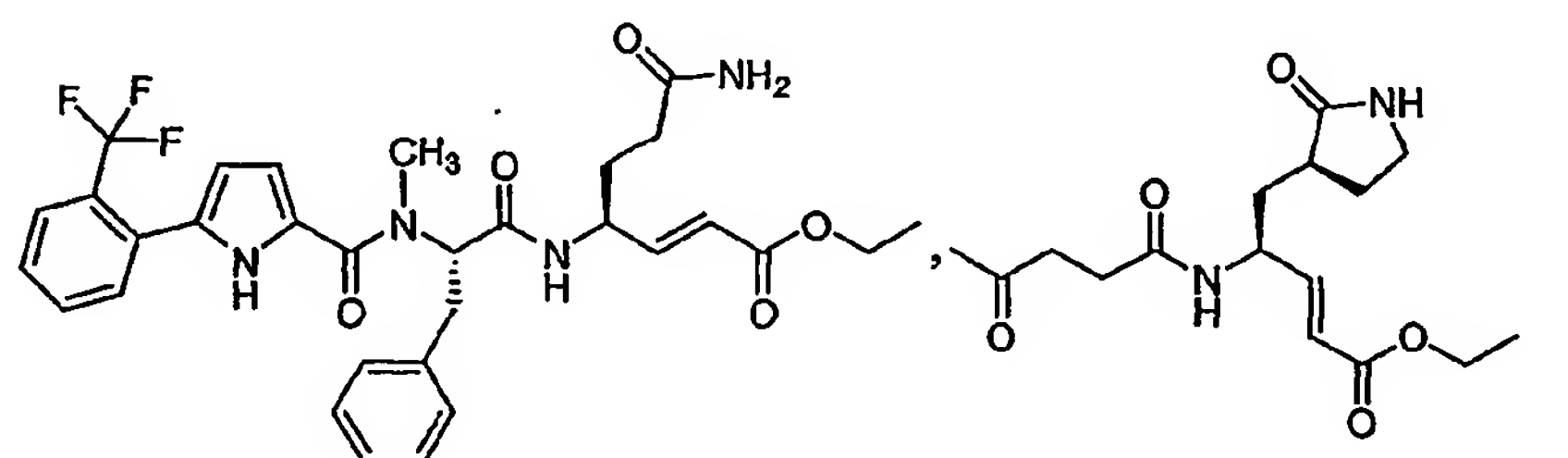
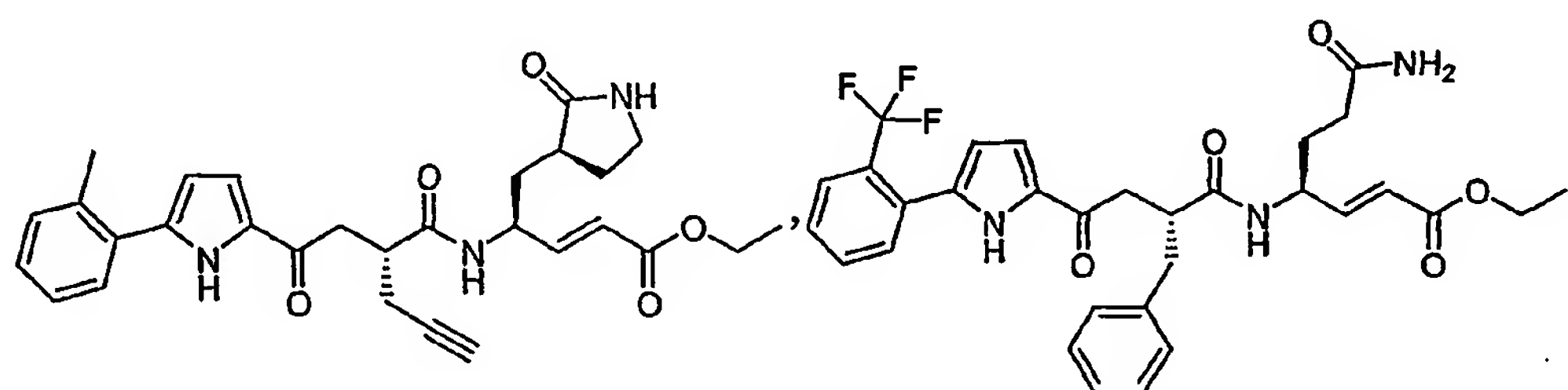
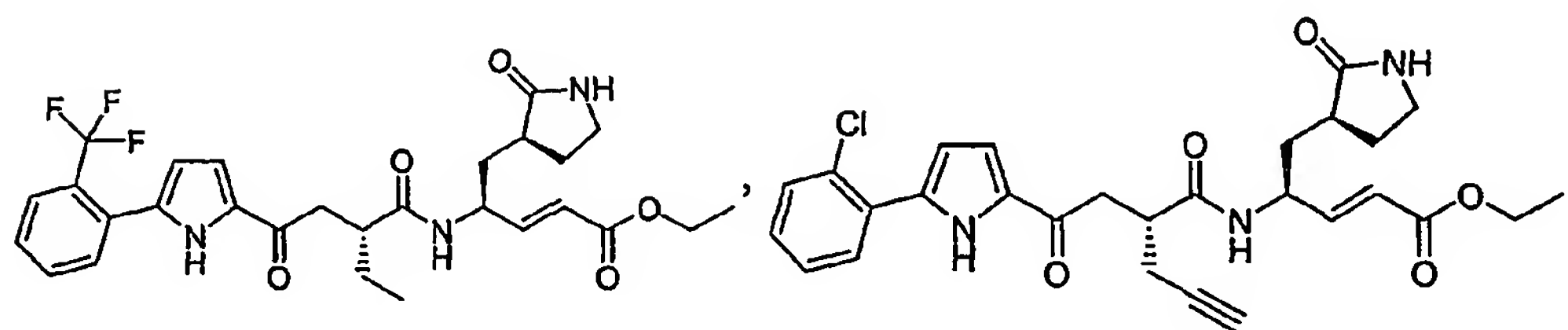
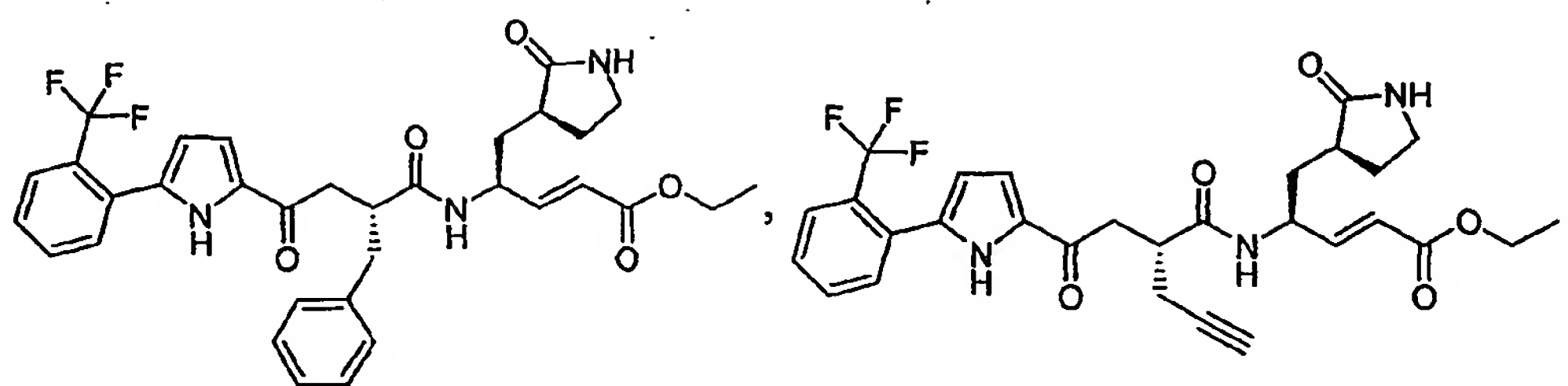
- 201 -





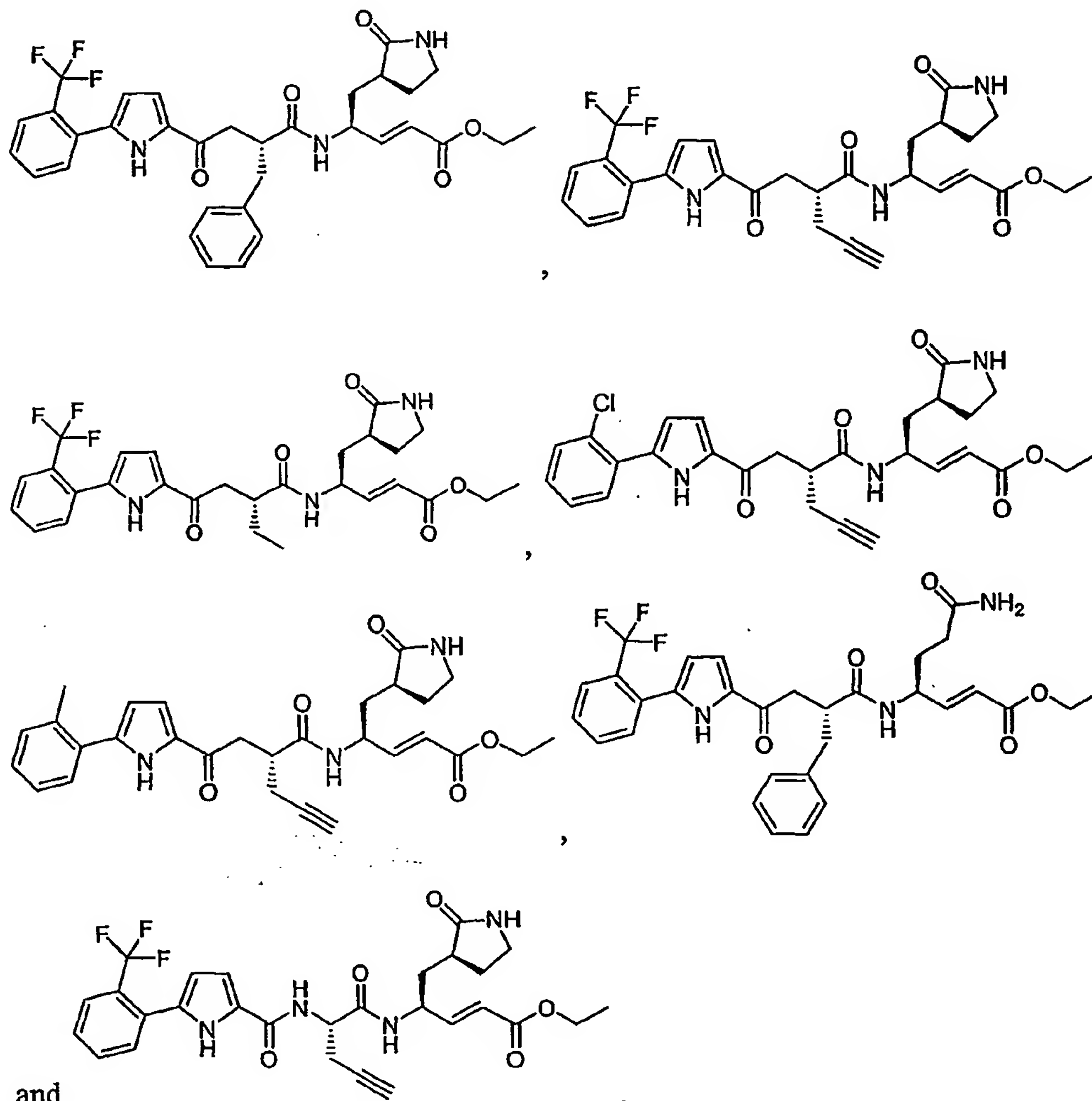


- 204 -



and

87. The compound according to claim 86, selected from the group consisting of:



(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
25 October 2001 (25.10.2001)

PCT

(10) International Publication Number
WO 01/79167 A3

(51) International Patent Classification⁷: C07D 207/34, 401/04, 405/14, 413/04, 405/14, 207/32, 207/26, 403/12, C07K 5/078, A61K 31/40, 31/4015, 31/4025, 38/05, 31/16

(74) Agents: SIEBURTH, Kathryn, L. et al.: Fitzpatrick, Cella, Harper & Scinto, 30 Rockefeller Plaza, New York, NY 10112-3801 (US).

(21) International Application Number: PCT/US01/12333

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(22) International Filing Date: 12 April 2001 (12.04.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/197,796 14 April 2000 (14.04.2000) US
60/198,497 18 April 2000 (18.04.2000) US

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant: AGOURON PHARMACEUTICALS, INC.
[US/US]; 10350 North Torrey Pines Road, La Jolla, CA 92037 (US).

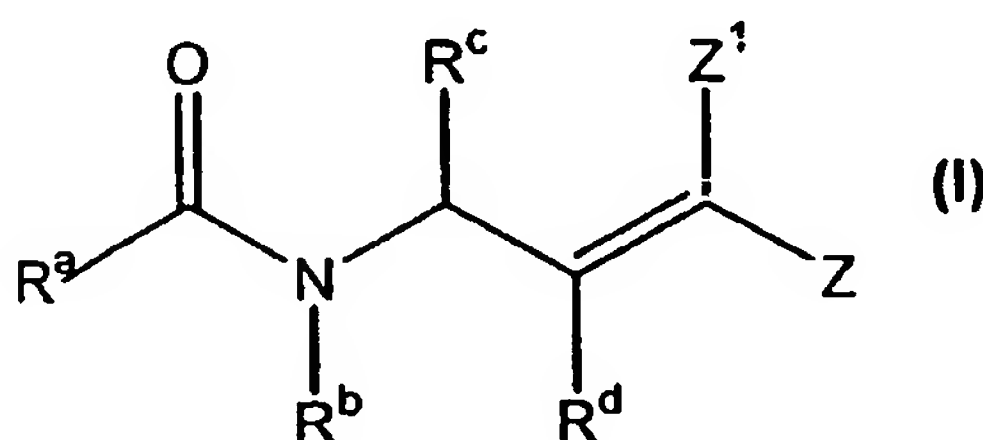
Published:
— with international search report

(72) Inventors: JOHNSON, Theodore, O., Jr.: 3612 Torrey View Court, San Diego, CA 92130 (US). HUA, Ye; 8671 Via Mallorca, Apt. #46, La Jolla, CA 92037 (US). LUU, Hiep, T.; 10330 Penrod Lane, San Diego, CA 92126 (US). DRAGOVICH, Peter, S.; 1372 Blue Heron Avenue, Encinitas, CA 92024 (US).

(88) Date of publication of the international search report:
28 February 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: ANTIPICORNAVIRAL COMPOUNDS AND COMPOSITIONS, THEIR PHARMACEUTICAL USES, AND MATERIALS FOR THEIR SYNTHESIS



(57) Abstract: Compounds of the formula (I) where the formula variables are as defined in the disclosure, advantageously inhibit or block the biological activity of the picornaviral 3C protease. These compounds, as well as pharmaceutical compositions containing these compounds, are useful for treating patients or hosts infected with one or more picornaviruses, such as RVP. Intermediates and synthetic methods for preparing such compounds are also described.



WO 01/79167 A3

INTERNATIONAL SEARCH REPORT

Int l Application No
PCT/US 01/12333

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D207/34 C07D401/04 C07D405/04 C07D413/04 C07D405/14
C07D207/32 C07D207/26 C07D403/12 C07K5/078 A61K31/40
A61K31/4015 A61K31/4025 A61K38/05 A61P31/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61P A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 43305 A (AGOURON PHARMA) 20 November 1997 (1997-11-20) claims 34-45; examples 1-190,8C page 21 -page 24 page 26; examples 29,44 page 27 -page 46 ---	1,8,13, 49,62, 76,80, 82-85
X	WO 99 57135 A (DRAGOVICH PETER SCOTT ; MARAKOVITS JOSEPH TIMOTHY (US); WEBBER STEP) 11 November 1999 (1999-11-11) compounds (A-1)-(A-28), (B-1)-(B-4) claims 22,67-70 examples 1-3 page 68, line 25 --- -/--	1,8,49, 62,76, 80,82-85

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

19 November 2001

Date of mailing of the international search report

03 12 2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, 1 x 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Seitner, I

INTERNATIONAL SEARCH REPORT

Int lional Application No
PCT/US 01/12333

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 43950 A (DRAGOVICH PETER S ;ZHOU RU (US); AGOURON PHARMA (US); PRINS THOMAS) 8 October 1998 (1998-10-08) cited in the application claims 25-34; examples 1-34 ---	1,80, 82-85
X	DRAGOVICH P S ET AL: "STRUCTURE-BASED DESIGN, SYNTHESIS, AND BIOLOGICAL EVALUATION OF IRREVERSIBLE HUMAN RHINOVIRUS 3C PROTEASE INHIBITORS. 4. INCORPORATION OF P1 LACTAM MOIEITES AS L-GLUTAMINE REPLACEMENTS" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 42, no. 7, 8 April 1999 (1999-04-08), pages 1213-1224, XP002153221 ISSN: 0022-2623 cited in the application abstract; examples 11,12,14,36,37 ---	1,8,49, 62,80, 82-85
X	DRAGOVICH P S ET AL: "Structure-based design, synthesis, and biological evaluation of irreversible human rhinovirus 3C protease inhibitors. 3. Structure-activity studies of ketomethylene-containing peptidomimetics" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 42, no. 7, 8 April 1999 (1999-04-08), pages 1203-1212, XP002153927 ISSN: 0022-2623 cited in the application the whole document examples 2-14,16 examples 1-8; tables 3-5 ---	1,80, 82-85
P,X	WO 01 10894 A (AGOURON PHARMA) 15 February 2001 (2001-02-15) claims 1,31-34 ---	1,80, 82-85
A	WO 98 04524 A (CALDARELLI MARINA ;BERIA ITALO (IT); COZZI PAOLO (IT); CAPOLOGO L) 5 February 1998 (1998-02-05) claims 1,7,9 ---	1,80, 82-85
A	WO 96 09822 A (SANOFI WINTHROP INC) 4 April 1996 (1996-04-04) claims 1,8-19 ---	1,80-85
	--- -/--	

INTERNATIONAL SEARCH REPORT

In. tional Application No

PCT/US 01/12333

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MOSS N ET AL: "PEPTIDOMIMETIC INHIBITORS OF HERPES SIMPLEX VIRUS RIBONUCLEOTIDE REDUCTASE WITH IMPROVED IN VIVO ANTIVIRAL ACTIVITY" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 39, no. 21, 11 October 1996 (1996-10-11), pages 4173-4180, XP002072015 ISSN: 0022-2623 the whole document	1,80, 82-85
X	WO 99 31122 A (AGOURON PHARMA) 24 June 1999 (1999-06-24) the whole document claims 29-34 page 21 -page 39	1,8,49, 62,82-85
X	WO 96 30395 A (WATANABE HIROYUKI ;FUJISAWA YUKIO (JP); FUKUDA TSUNEHICO (JP); TAK) 3 October 1996 (1996-10-03) examples 71,72,118,120,121	1,8,49, 62
X	DRAGOVICH P S ET AL: "Structure-based design, synthesis, and biological evaluation of irreversible human rhinovirus 3C protease inhibitors. 2. Peptide structure-activity studies" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 41, no. 15, 16 July 1998 (1998-07-16), pages 2819-2834, XP002100727 ISSN: 0022-2623 the whole document	1,8,49, 62,82-85
X	DRAGOVICH P S ET AL: "SOLID-PHASE SYNTHESIS OF IRREVERISBLE HUMAN RHINOVIRUS 3C PROTEASE INHIBITORS. PART 1: OPTIMIZATION OF TRIPEPTIDES INCORPORATING N-TERMINAL AMIDES" BIOORGANIC & MEDICINAL CHEMISTRY, ELSEVIER SCIENCE LTD, GB, vol. 7, no. 4, 1999, pages 589-598, XP000885728 ISSN: 0968-0896 cited in the application the whole document	1,8,49, 62,82-85

-/-

INTERNATIONAL SEARCH REPORT

In .tional Application No
PCT/US 01/12333

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DRAGOVICH P S ET AL: "Structure-based design of irreversible, tripeptidyl human rhinovirus 3C protease inhibitors containing N-methyl amino acids" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 9, no. 15, 2 August 1999 (1999-08-02), pages 2189-2194, XP004174157 ISSN: 0960-894X the whole document</p> <p>-----</p>	<p>1,8,49, 62,82-85</p>

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/12333

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 83-85 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1-48,80-85 (all partially)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid. Specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-3, 6, 7, 40, 49-51, 80, 82-85 (all partially)

Compounds according to the formula of claim 1 for which Ra is alkylcarbonylalkyl and Rc forms an acyclic moiety as well as their pharmaceutical use and compositions.

2. Claims: 1-3, 6-10, 21, 22, 24-27, 29, 30, 32-34, 37, 38, 40-43, 49-54, 62-65, 79, 80, 82-86 (all partially)

Compounds according to the formula of claim 1 for which Ra is alkylcarbonylalkyl and Rc forms a cyclic moiety as well as their pharmaceutical use and compositions.

3. Claims: 1-3, 6-10 (all partially); 12 (completely); 16-18, 21-35, 37-43 (all partially); 45 (completely); 49-54, 61-65 (all partially); 67 (completely); 79-87 (all partially)

Compounds according to the formula of claim 1 for which Ra is cycloalkylcarbonylalkyl, arylcarbonylalkyl, or heteroarylcarbonyl as well as their pharmaceutical use and compositions.

4. Claims: 1, 2, 4, 6, 7, 40, 49-51, 80, 82-85 (all partially)

Compounds according to the formula of claim 1 for which Ra is alkylcarbonylaminoalkyl and Rc forms an acyclic moiety as well as their pharmaceutical use and compositions.

5. Claims: 1, 2, 4, 6-9, 11, 21, 22, 24-27, 29-34, 37, 38, 40-42, 44, 49-51, 55, 61-64, 66, 79, 80, 82-85 (all partially)

Compounds according to the formula of claim 1 for which Ra is alkylcarbonylaminoalkyl and Rc forms a cyclic moiety as well as their pharmaceutical use and compositions.

6. Claims: 1, 2, 4, 6, 7, 13, 16-18, 21-31, 33, 35, 37, 39-42, 46, 48-51, 70-72, 79-86 (all partially)

Compounds according to the formula of claim 1 for which Ra

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

is cycloalkylcarbonylaminoalkyl, heterocycloalkylcarbonylaminoalkyl, arylcarbonylaminoalkyl, heteroarylcarbonylaminoalkyl and Rc forms an acyclic moiety as well as their pharmaceutical use and compositions.

7. Claims: 1, 2, 4, 6-9, 11, 13 (all partially); 14, 15 (all completely); 16-18, 21-35, 37-42, 44, 46 (all partially); 47 (completely); 48-51, 55 (all partially); 56, 57 (all completely); 61-64, 66, 70-72 (all partially); 73-75 (all completely); 79-87 (all partially)

Compounds according to the formula of claim 1 for which Ra is cycloalkylcarbonylaminoalkyl, heterocycloalkylcarbonylaminoalkyl, arylcarbonylaminoalkyl, heteroarylcarbonylaminoalkyl and Rc forms a cyclic moiety as well as their pharmaceutical use and compositions.

8. Claims: 1, 2 (all partially); 5 (completely); 6, 7 (all partially); 19, 20 (all completely); 21, 22, 24-27, 29, 30, 32, 33 (all partially); 36 (completely); 37, 40-42, 49-51 (all partially); 58-60 (all completely); 61 (partially); 76-78 (all completely); 79, 80, 82-86 (all partially)

Compounds according to the formula of claim 1 for which Ra is alkylaminocarbonylalkyl, cycloalkylaminocarbonylalkyl, heterocycloalkylaminocarbonylalkyl, arylaminocarbonylalkyl, or heteroarylaminocarbonylalkyl as well as their pharmaceutical use and compositions.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-48,80-85 (all partially)

The scope of claims 1-48 and 80-85, in as far as the expressions "prodrugs" and "pharmaceutically active metabolite" (see claim 1, page 148, lines 3 and 4) are concerned, is so unclear (Article 6 PCT) that a meaningful International Search is impossible with regard to these expressions.

Nevertheless, the search was complete for derivatives of one of the compounds of the present application that contain the moieties selected from -COOR, -PO(OR)₂, or -C=NR (see page 74, line 8).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/12333

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9743305	A	20-11-1997	US 5856530 A	05-01-1999
			AU 722704 B2	10-08-2000
			AU 3005997 A	05-12-1997
			CA 2254343 A1	20-11-1997
			EP 0910572 A1	28-04-1999
			JP 2000506903 T	06-06-2000
			WO 9743305 A1	20-11-1997
			US 6214799 B1	10-04-2001
			ZA 9704108 A	20-08-1998
WO 9957135	A	11-11-1999	AU 2028799 A	23-11-1999
			BG 104899 A	31-08-2001
			BR 9910573 A	16-01-2001
			CN 1311793 T	05-09-2001
			EP 1073672 A1	07-02-2001
			HR 20000623 A1	30-04-2001
			NO 20005411 A	27-10-2000
			SI 20428 A	30-06-2001
			WO 9957135 A1	11-11-1999
WO 9843950	A	08-10-1998	US 6020371 A	01-02-2000
			AU 736550 B2	02-08-2001
			AU 6778898 A	22-10-1998
			EP 0975588 A1	02-02-2000
			WO 9843950 A1	08-10-1998
WO 0110894	A	15-02-2001	AU 6511200 A	05-03-2001
			WO 0110894 A2	15-02-2001
WO 9804524	A	05-02-1998	AT 205476 T	15-09-2001
			AU 724511 B2	21-09-2000
			AU 4009897 A	20-02-1998
			BR 9710717 A	17-08-1999
			CA 2260060 A1	05-02-1998
			CN 1226232 A	18-08-1999
			DE 69706690 D1	18-10-2001
			WO 9804524 A1	05-02-1998
			EP 0915845 A1	19-05-1999
			JP 2000515164 T	14-11-2000
			NO 990246 A	20-01-1999
			NZ 334082 A	30-08-1999
			PL 331344 A1	05-07-1999
WO 9609822	A	04-04-1996	US 5523312 A	04-06-1996
			AU 3554995 A	19-04-1996
			CA 2199275 A1	04-04-1996
			WO 9609822 A1	04-04-1996
			US 5514692 A	07-05-1996
WO 9931122	A	24-06-1999	US 5962487 A	05-10-1999
			AU 1826299 A	05-07-1999
			BR 9813651 A	03-10-2000
			EP 1037905 A1	27-09-2000
			HU 0100149 A2	28-06-2001
			NO 20003067 A	15-08-2000
			PL 341435 A1	09-04-2001
			WO 9931122 A1	24-06-1999

INTERNATIONAL SEARCH REPORT

Information on patent family members

In. tional Application No

PCT/US 01/12333

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9630395	A	03-10-1996	
		AU 5122196 A	16-10-1996
		CA 2215211 A1	03-10-1996
		EP 0820464 A2	28-01-1998
		JP 9165360 A	24-06-1997
		WO 9630395 A2	03-10-1996
		US 6162828 A	19-12-2000